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CODING SEQUENCES OF THE HUMAN BRCA1 GENE

5

FIELD OF THE INVENTION

This invention relates to a gene which has been associated with breast and ovarian cancer where the gene is found to be mutated. More specifically, this invention relates to the three coding sequences of the BRCA1 gene BRCA1^(omi1),
10 BRCA1^(omi2), and BRCA1^(omi3) isolated from human subjects.

BACKGROUND OF THE INVENTION

It has been estimated that about 5-10% of breast cancer is inherited Rowell, S., *et al.*, *American Journal of Human Genetics* 55:861-865 (1994). Located on
15 chromosome 17, BRCA1 is the first gene identified to be conferring increased risk for breast and ovarian cancer. Miki *et al.*, *Science* 266:66-71 (1994). Mutations in this "tumor suppressor" gene are thought to account for roughly 45% of inherited breast cancer and 80-90% of families with increased risk of early onset breast and ovarian cancer. Easton *et al.*, *American Journal of Human Genetics* 52:678-701 (1993).
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Locating one or more mutations in the BRCA1 region of chromosome 17 provides a promising approach to reducing the high incidence and mortality associated with breast and ovarian cancer through the early detection of women at high risk. These women, once identified, can be targeted for more aggressive
25 prevention programs. Screening is carried out by a variety of methods which include karyotyping, probe binding and DNA sequencing.

In DNA sequencing technology, genomic DNA is extracted from whole blood and the coding sequences of the BRCA1 gene are amplified. The coding sequences might be sequenced completely and the results are compared to the
30 DNA sequence of the gene. Alternatively, the coding sequence of the sample gene may be compared to a panel of known mutations before completely sequencing the gene and comparing it to a normal sequence of the gene.

If a mutation in the BRCA1 coding sequence is found, it may be possible to provide the individual with increased expression of the gene through gene transfer therapy. It has been demonstrated that the gene transfer of the BRCA1 coding sequence into cancer cells inhibits their growth and reduces tumorigenesis of human cancer cells in nude mice. Jeffrey Holt and his colleagues conclude that the product of BRCA1 expression is a secreted tumor growth inhibitor, making BRCA1 an ideal gene for gene therapy studies. Transduction of only a moderate percentage of tumor cells apparently produces enough growth inhibitor to inhibit all tumor cells. Arteaga, CL, and JT Holt Cancer Research 56: 1098-1103 (1996), Holt, JT et al., Nature Genetics 12: 298-302 (1996).

The observation of Holt et al, that the BRCA1 growth inhibitor is a secreted protein leads to the possible use of injection of the growth inhibitor into the area of the tumor for tumor suppression.

The BRCA1 gene is divided into 24 separate exons. Exons 1 and 4 are noncoding, in that they are not part of the final functional BRCA1 protein product. The BRCA1 coding sequence spans roughly 5600 base pairs (bp). Each exon consists of 200-400 bp, except for exon 11 which contains about 3600 bp. To sequence the coding sequence of the BRCA1 gene, each exon is amplified separately and the resulting PCR products are sequenced in the forward and reverse directions. Because exon 11 is so large, we have divided it into twelve overlapping PCR fragments of roughly 350 bp each (segments "A" through "L" of BRCA1 exon 11).

Many mutations and polymorphisms have already been reported in the BRCA1 gene. A world wide web site has been built to facilitate the detection and characterization of alterations in breast cancer susceptibility genes. Such mutations in BRCA1 can be accessed through the Breast Cancer Information Core at: http://www.nchgr.nih.gov/dir/lab_transfer/bic. This data site became publicly available on November 1, 1995. Friend, S. et al. Nature Genetics 11:238, (1995).

The genetics of Breast/Ovarian Cancer Syndrome is autosomal dominant with reduced penetrance. In simple terms, this means that the syndrome runs through families such that both sexes can be carriers (only women get the disease but men can pass it on), all generations will likely have breast/ovarian or both diseases and sometimes in the same individual, occasionally women carriers either die young before they have the time to manifest disease (and yet offspring get it) or they never develop breast or ovarian cancer and die of old age (the latter people are said to have "reduced penetrance" because they never develop cancer). Pedigree analysis and genetic counseling is absolutely essential to the proper workup of a family prior to any lab work.

Until now, only a single coding sequence for the BRCA1 gene has been available for comparison to patient samples. That sequence is available as GenBank Accession Number U14680. There is a need in the art, therefore, to have available a coding sequence which is the BRCA1 coding sequence found in the majority of the population, a "consensus coding sequence", BRCA1^(omi1) Seq. ID. NO. 1. A consensus coding sequence will make it possible for true mutations to be easily identified or differentiated from polymorphisms. Identification of mutations of the BRCA1 gene and protein would allow more widespread diagnostic screening for hereditary breast and ovarian cancer than is currently possible. Two additional coding sequences have been isolated and characterized. The BRCA1^(omi2) Seq. ID. NO.: 3, and BRCA1^(omi3) Seq. ID. NO.:5 coding sequences also have utility in diagnosis, gene therapy and in making therapeutic BRCA1 protein.

A coding sequence of the BRCA1 gene which occurs most commonly in the human gene pool is provided. The most commonly occurring coding sequence more accurately reflects the most likely sequence to be found in a subject. Use of the coding sequence BRCA1^(omi1) Seq. ID. NO.: 1, rather than the previously published BRCA1 sequence, will reduce the likelihood of misinterpreting a "sequence variation" found in the population (i.e. polymorphism) with a pathologic "mutation" (i.e. causes disease in the individual or puts the individual at a high risk of developing the disease). With large interest in breast cancer predisposition testing, misinterpretation is

particularly worrisome. People who already have breast cancer are asking the clinical question: "is my disease caused by a heritable genetic mutation?" The relatives of the those with breast cancer are asking the question: "Am I also a carrier of the mutation my relative has? Thus, is my risk increased, and should I
5 undergo a more aggressive surveillance program."

SUMMARY OF THE INVENTION

The present invention is based on the isolation of three coding sequences of the BRCA1 gene found in human individuals.

10 It is an object of the invention to provide the most commonly occurring coding sequence of the BRCA1 gene.

It is another object of this invention to provide two other coding sequences of BRCA1 gene.

15 It is another object of the invention to provide three protein sequences coded for by three of the coding sequences of the BRCA1 gene.

It is another object of the invention to provide a list of the codon pairs which occur at each of seven polymorphic points on the BRCA1 gene.

It is another object of the invention to provide the rates of occurrence for the codons.

20 It is another object of the invention to provide a method wherein BRCA1, or parts thereof, is amplified with one or more oligonucleotide primers.

25 It is another object of this invention to provide a method of identifying individuals who carry no mutation(s) of the BRCA1 coding sequence and therefore have no increased genetic susceptibility to breast or ovarian cancer based on their BRCA1 genes.

It is another object of this invention to provide a method of identifying a mutation leading to an increased genetic susceptibility to breast or ovarian cancer.

30 There is a need in the art for a sequence of the BRCA1 gene and for the protein sequence of BRCA1 as well as for an accurate list of codons which occur at polymorphic points on a sequence.

A person skilled in the art of genetic susceptibility testing will find the present invention useful for:

- a) identifying individuals having a BRCA1 gene with no coding mutations, who therefore cannot be said to have an increased genetic susceptibility to breast or ovarian cancer from their BRCA1 genes;
- b) avoiding misinterpretation of polymorphisms found in the BRCA1 gene;
- c) determining the presence of a previously unknown mutation in the BRCA1 gene.
- d) identifying a mutation which increases the genetic susceptibility to breast or ovarian cancer.
- e) probing a human sample of the BRCA1 gene.
- f) performing gene therapy.
- g) for making a functioning tumor growth inhibitor protein coded for by one of the BRCA1^{omi} genes.

BRIEF DESCRIPTION OF THE FIGURE

As shown in FIGURE 1, the alternative alleles at polymorphic (non-mutation causing variations) sites along a chromosome can be represented as a "haplotype" within a gene such as BRCA1. The BRCA1^(omi1) haplotype is shown in Figure 1 with dark shading (encompassing the alternative alleles found at nucleotide sites 2201, 2430, 2731, 3232, 3667, 4427, and 4956). For comparison, the haplotype that is in GenBank is shown with no shading. As can be seen from the figure, the common "consensus" haplotype is found intact in five separate chromosomes labeled with the OMI symbol (numbers 1-5 from left to right). Two additional haplotypes (BRCA1^(omi2), and BRCA1^(omi3)) are represented with mixed dark and light shading (numbers 7 and 9 from left to right). In total, 7 of 10 haplotypes along the BRCA1 gene are unique.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The following definitions are provided for the purpose of understanding this invention.

"Breast and Ovarian cancer" is understood by those skilled in the art to include breast and ovarian cancer in women and also breast and prostate cancer in men. BRCA1 is associated genetic susceptibility to inherited breast and ovarian cancer in women and also breast and prostate cancer in men. Therefore, claims in this document which recite breast and/or ovarian cancer refer to breast, ovarian and prostate cancers in men and women.

" Coding sequence" or " DNA coding sequence" refers to those portions of a gene which, taken together, code for a peptide (protein), or which nucleic acid itself has function.

" Protein" or "peptide" refers to a sequence amino acids which has function.

"BRCA1(omi)" refers collectively to the "BRCA1(omi1)", "BRCA1(omi2)" and "BRCA1(omi3)" coding sequences.

"BRCA1(omi1)" refers to SEQ. ID. NO.: 1, a coding sequence for the BRCA1 gene. The coding sequence was found by end to end sequencing of BRCA1 alleles from individuals randomly drawn from a Caucasian population found to have no family history of breast or ovarian cancer. The sequenced gene was found not to contain any mutations. BRCA1(omi1) was determined to be a consensus sequence by calculating the frequency with which the coding sequence occurred among the sample alleles sequenced.

"BRCA1(omi2)" and "BRCA1(omi3)" refer to SEQ. ID. NO.: 3, and SEQ. ID. NO.: 5 respectively. They are two additional coding sequences for the BRCA1 gene

which were also isolated from individuals randomly drawn from a Caucasian population found to have no family history of breast or ovarian cancer. polymorphisms

5 "Primer" as used herein refers to a sequence comprising about 20 or more nucleotides of the BRCA1 gene.

"Genetic susceptibility" refers to the susceptibility to breast or ovarian cancer due to the presence of a mutation in the BRCA1 gene.

10 A "target polynucleotide" refers to the nucleic acid sequence of interest *e.g.*, the BRCA1 encoding polynucleotide. Other primers which can be used for primer hybridization will be known or readily ascertainable to those of skill in the art.

15 "Consensus" means the most commonly occurring in the population.

"Consensus genomic sequence" means the allele of the target gene which occurs with the greatest frequency in a population of individuals having no family history of disease associated with the target gene.

20 "Substantially complementary to" refers to a probe or primer sequences which hybridize to the sequences provided under stringent conditions and/or sequences having sufficient homology with BRCA1 sequences, such that the allele specific oligonucleotide probe or primers hybridize to the BRCA1 sequences to which they are complimentary.

"Haplotype" refers to a series of alleles within a gene on a chromosome.

30 "Isolated" as used herein refers to substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with which they may be associated. Such association is typically either in cellular material or in a synthesis medium.

"Mutation" refers to a base change or a gain or loss of base pair(s) in a DNA sequence, which results in a DNA sequence which codes for a non-functioning protein or a protein with substantially reduced or altered function.

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"Polymorphism" refers to a base change which is not associated with known pathology.

10 "Tumor growth inhibitor protein" refers to the protein coded for by the BRCA1 gene. The functional protein is thought to suppress breast and ovarian tumor growth.

The invention in several of its embodiments includes:

1. An isolated consensus DNA sequence of the BRCA1 coding sequence as set forth in SEQ. ID. NO.: 1.

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2. A consensus protein sequence of the BRCA1 protein as set forth in SEQ. ID. NO.: 2.

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3. An isolated coding sequence of the BRCA1 gene as set forth in SEQ. ID. NO.: 3.

4. A protein sequence of the BRCA1 protein as set forth in SEQ. ID. NO.: 4 .

25 5. An isolated coding sequence of the BRCA1 gene as set forth in SEQ. ID. NO.: 5.

6. A protein sequence of the BRCA1 protein as set forth in SEQ. ID. NO.: 6.

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7. A BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer which comprises an alternative pair of codons, AGC

and AGT, which occur at position 2201 at frequencies of about 35-45%, and from about 55-65%, respectively.

5 8. A BRCA1 gene according to Claim 7 wherein AGC occurs at a frequency of about 40%.

10 9. A set of at least two alternative codon pairs which occur at polymorphic positions in a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer, wherein codon pairs are selected from the group consisting of:

- AGC and AGT at position 2201;
- TTG and CTG at position 2430;
- CCG and CTG at position 2731;
- GAA and GGA at position 3232;
- 15 • AAA and AGA at position 3667;
- TCT and TCC at position 4427; and
- AGT and GGT at position 4956.

20 10. A set of at least two alternative codon pairs according to claim 9, wherein the codon pairs occur in the following frequencies, respectively, in a population of individuals free of disease:

- at position 2201, AGC and AGT occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- 25 • at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- 30 • at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about

35-45%, and from about 55-65%, respectively.

11 A set according to Claim 10 which is at least three codon pairs.

5 12 A set according to Claim 10 which is at least four codon pairs.

13. A set according to Claim 10 which is at least five codon pairs.

14. A set according to Claim 10 which is at least six codon pairs.

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15 A set according to Claim 10 which is at least seven codon pairs.

16. A method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with disease, comprising:

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(a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;

(b) sequencing said amplified DNA fragment by dideoxy sequencing;

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(c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;

(d) comparing the sequence of said amplified DNA fragment to a BRCA1^(oml) DNA sequence, SEQ. ID. NO1, SEQ. ID. NO3, or SEQ. ID. NO5;

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(e) determining the presence or absence of each of the following polymorphic variation in said individual's BRCA1 coding sequence:

- AGC and AGT at position 2201,
- TTG and CTG at position 2430,
- CCG and CTG at position 2731,
- GAA and GGA at position 3232,
- AAA and AGA at position 3667,
- TCT and TCC at position 4427, and
- AGT and GGT at position 4956;

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(f) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO1, SEQ. ID. NO3, or SEQ. ID. NO5 wherein the presence of said polymorphic variations and the absence of a variation outside of positions 2201, 2430, 2731, 3232, 3667, 4427, and 4956, is correlated with an absence of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

17. A method of claim 16 wherein, codon variations occur at the following frequencies, respectively, in a population of individuals free of disease:

- at position 2201, AGC and AGT occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about 35-45%, and from about 55-65%, respectively.

18. A method according to claim 16 wherein said oligonucleotide primer is labeled with a radiolabel, a fluorescent label a bioluminescent label, a chemiluminescent label, or an enzyme label.

19. A method of detecting a increased genetic susceptibility to breast and

ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising:

- (a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;
- (b) sequencing said amplified DNA fragment by dideoxy sequencing;
- (c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;
- (d) comparing the sequence of said amplified DNA fragment to a BRCA1^(omi) DNA sequence, SEQ. ID. NO1, SEQ. ID. NO3, or SEQ. ID. NO5;
- (e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO1, SEQ. ID. NO3, or SEQ. ID. NO5; to determine the presence or absence of base changes in said individual's BRCA1 coding sequence wherein a base change which is not any one of the following:
 - AGC and AGT at position 2201,
 - TTG and CTG at position 2430,
 - CCG and CTG at position 2731,
 - GAA and GGA at position 3232,
 - AAA and AGA at position 3667,
 - TCT and TCC at position 4427, and
 - AGT and GGT at position 4956 is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.

20. A method of claim 19 wherein, codon variations occur at the following frequencies, respectively, in a population free of disease:

- at position 2201, AGC and AGT occur at frequencies from about 40%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about

35-45%, and from about 55-65%, respectively;

- at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about 35-45%, and from about 55-65%, respectively.

21. A method according to claim 19 wherein said oligonucleotide primer is labeled with a radiolabel, a fluorescent label a bioluminescent label, a chemiluminescent label, or an enzyme label.

22. A set of codon pairs, which occur at polymorphic positions in a BRCA1 gene with a BRCA1 coding sequence according to Claim 1, wherein said set of codon pairs is:

- AGC and AGT at position 2201;
- TTG and CTG at position 2430;
- CCG and CTG at position 2731;
- GAA and GGA at position 3232;
- AAA and AGA at position 3667;
- TCT and TCC at position 4427; and
- AGT and GGT at position 4956.

23. A set of at least two alternative codon pairs according to claim 22 wherein set of at least two alternative codon pairs occur at the following frequencies:

- at position 2201, AGC and AGT occur at frequencies of about 40%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about 35-45%, and from about 55-65%, respectively;

- at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about 35-45%, and from about 55-65%, respectively.

24. A BRCA1 coding sequence according to claim 1 wherein the codon pairs occur at the following frequencies:

- at position 2201, AGC and AGT occur at frequencies of about 40%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about 35-45%, and from about 55-65%, respectively.

25. A method of determining the consensus genomic sequence or consensus coding sequence for a target gene, comprising:

- a) screening a number of individuals in a population for a family history which indicates inheritance of normal alleles for a target gene;
- b) isolating at least one allele of the target gene from individuals found to

have a family history which indicates inheritance of normal alleles for a target gene;

c) sequencing each allele;

d) comparing the nucleic acid sequence of the genomic sequence or of the coding sequence of each allele of the target gene to determine similarities and differences in the nucleic acid sequence; and

e) determining which allele of the target gene occurs with the greatest frequency.

26. A method of performing gene therapy, comprising:

a) transfecting cancer cell *in vivo* with an effective amount of a vector transformed with a BRCA1 coding sequences of SEQ. ID. NO.: 1, SEQ. ID. NO.: 3, or SEQ. ID. NO.: 5;

b) allowing the cells to take up the vector, and

c) measuring a reduction in tumor growth.

27. A method of performing protein therapy, comprising:

a) injecting into a patient, an effective amount of BRCA1 tumor growth inhibiting protein of SEQ. ID. NO.: 2, SEQ. ID. NO.: 4, or SEQ. ID. NO.: 6;

b) allowing the cells to take up the protein, and

c) measuring a reduction in tumor growth.

SEQUENCING

Any nucleic acid specimen, in purified or non-purified form, can be utilized as the starting nucleic acid or acids, providing it contains, or is suspected of containing, the specific nucleic acid sequence containing a polymorphic locus. Thus, the process may amplify, for example, DNA or RNA, including messenger RNA, wherein DNA or RNA may be single stranded or double stranded. In the event that RNA is to be used as a template, enzymes, and/or conditions optimal for reverse transcribing the template to DNA would be utilized. In addition, a DNA-RNA hybrid which contains one strand of each may be utilized. A mixture

of nucleic acids may also be employed, or the nucleic acids produced in a previous amplification reaction herein, using the same or different primers may be so utilized. See TABLE II. The specific nucleic acid sequence to be amplified, *i.e.*, the polymorphic locus, may be a fraction of a larger molecule or can be present initially as a discrete molecule, so that the specific sequence constitutes the entire nucleic acid. It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture, such as contained in whole human DNA.

DNA utilized herein may be extracted from a body sample, such as blood, tissue material and the like by a variety of techniques such as that described by Maniatis, *et. al.* in *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor, NY, p 280-281, 1982). If the extracted sample is impure, it may be treated before amplification with an amount of a reagent effective to open the cells, or animal cell membranes of the sample, and to expose and/or separate the strand(s) of the nucleic acid(s). This lysing and nucleic acid denaturing step to expose and separate the strands will allow amplification to occur much more readily.

The deoxyribonucleotide triphosphates dATP, dCTP, dGTP, and dTTP are added to the synthesis mixture, either separately or together with the primers, in adequate amounts and the resulting solution is heated to about 90°-100°C from about 1 to 10 minutes, preferably from 1 to 4 minutes. After this heating period, the solution is allowed to cool, which is preferable for the primer hybridization. To the cooled mixture is added an appropriate agent for effecting the primer extension reaction (called herein "agent for polymerization"), and the reaction is allowed to occur under conditions known in the art. The agent for polymerization may also be added together with the other reagents if it is heat stable. This synthesis (or amplification) reaction may occur at room temperature up to a temperature above which the agent for polymerization no longer functions. Thus, for example, if DNA polymerase is used as the agent, the temperature is generally no greater than about 40°C. Most conveniently the reaction occurs at room temperature.

The primers used to carry out this invention embrace oligonucleotides of

sufficient length and appropriate sequence to provide initiation of polymerization. Environmental conditions conducive to synthesis include the presence of nucleoside triphosphates and an agent for polymerization, such as DNA polymerase, and a suitable temperature and pH. The primer is preferably
5 single stranded for maximum efficiency in amplification, but may be double stranded. If double stranded, the primer is first treated to separate its strands before being used to prepare extension products. The primer must be sufficiently long to prime the synthesis of extension products in the presence of the inducing agent for polymerization. The exact length of primer will depend on many
10 factors, including temperature, buffer, and nucleotide composition. The oligonucleotide primer typically contains 12-20 or more nucleotides, although it may contain fewer nucleotides.

Primers used to carry out this invention are designed to be substantially complementary to each strand of the genomic locus to be amplified. This means
15 that the primers must be sufficiently complementary to hybridize with their respective strands under conditions which allow the agent for polymerization to perform. In other words, the primers should have sufficient complementarity with the 5' and 3' sequences flanking the mutation to hybridize therewith and permit amplification of the genomic locus.

20 Oligonucleotide primers of the invention are employed in the amplification process which is an enzymatic chain reaction that produces exponential quantities of polymorphic locus relative to the number of reaction steps involved. Typically, one primer is complementary to the negative (-) strand of the polymorphic locus and the other is complementary to the positive
25 (+) strand. Annealing the primers to denatured nucleic acid followed by extension with an enzyme, such as the large fragment of DNA polymerase I (Klenow) and nucleotides, results in newly synthesized + and - strands containing the target polymorphic locus sequence. Because these newly synthesized sequences are also templates, repeated cycles of denaturing, primer
30 annealing, and extension results in exponential production of the region (*i.e.*, the target polymorphic locus sequence) defined by the primers. The product of the chain reaction is a discrete nucleic acid duplex with termini corresponding to the

ends of the specific primers employed.

The oligonucleotide primers of the invention may be prepared using any suitable method, such as conventional phosphotriester and phosphodiester methods or automated embodiments thereof. In one such automated
5 embodiment, diethylphosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., Tetrahedron Letters, 22:1859-1862, 1981. One method for synthesizing oligonucleotides on a modified solid support is described in U.S. Patent No. 4,458,066.

10 The agent for polymerization may be any compound or system which will function to accomplish the synthesis of primer extension products, including enzymes. Suitable enzymes for this purpose include, for example, *E. coli* DNA polymerase I, Klenow fragment of *E. coli* DNA polymerase, polymerase muteins, reverse transcriptase, other enzymes, including heat-stable enzymes (*e.i.*, those
15 enzymes which perform primer extension after being subjected to temperatures sufficiently elevated to cause denaturation), such as *Taq* polymerase. Suitable enzyme will facilitate combination of the nucleotides in the proper manner to form the primer extension products which are complementary to each polymorphic locus nucleic acid strand. Generally, the synthesis will be initiated
20 at the 3' end of each primer and proceed in the 5' direction along the template strand, until synthesis terminates, producing molecules of different lengths.

The newly synthesized strand and its complementary nucleic acid strand will form a double-stranded molecule under hybridizing conditions described above and this hybrid is used in subsequent steps of the process. In the next step,
25 the newly synthesized double-stranded molecule is subjected to denaturing conditions using any of the procedures described above to provide single-stranded molecules.

The steps of denaturing, annealing, and extension product synthesis can be repeated as often as needed to amplify the target polymorphic locus nucleic acid
30 sequence to the extent necessary for detection. The amount of the specific nucleic acid sequence produced will accumulate in an exponential fashion. Amplification is described in PCR. A Practical Approach, ILR Press, Eds. M. J.

McPherson, P. Quirke, and G. R. Taylor, 1992.

The amplification products may be detected by Southern blots analysis, without using radioactive probes. In such a process, for example, a small sample of DNA containing a very low level of the nucleic acid sequence of the polymorphic locus is amplified, and analyzed via a Southern blotting technique or similarly, using dot blot analysis. The use of non-radioactive probes or labels is facilitated by the high level of the amplified signal. Alternatively, probes used to detect the amplified products can be directly or indirectly detectably labeled, for example, with a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator or an enzyme. Those of ordinary skill in the art will know of other suitable labels for binding to the probe, or will be able to ascertain such, using routine experimentation.

Sequences amplified by the methods of the invention can be further evaluated, detected, cloned, sequenced, and the like, either in solution or after binding to a solid support, by any method usually applied to the detection of a specific DNA sequence such as PCR, oligomer restriction (Saiki, *et.al.*, *Bio/Technology*, 3:1008-1012, 1985), allele-specific oligonucleotide (ASO) probe analysis (Conner, *et. al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 80:278, 1983), oligonucleotide ligation assays (OLAs) (Landgren, *et. al.*, *Science*, 241:1007, 1988), and the like. Molecular techniques for DNA analysis have been reviewed (Landgren, *et. al.*, *Science*, 242:229-237, 1988).

Preferably, the method of amplifying is by PCR, as described herein and as is commonly used by those of ordinary skill in the art. Alternative methods of amplification have been described and can also be employed as long as the BRCA1 locus amplified by PCR using primers of the invention is similarly amplified by the alternative means. Such alternative amplification systems include but are not limited to self-sustained sequence replication, which begins with a short sequence of RNA of interest and a T7 promoter. Reverse transcriptase copies the RNA into cDNA and degrades the RNA, followed by reverse transcriptase polymerizing a second strand of DNA. Another nucleic acid amplification technique is nucleic acid sequence-based amplification (NASBA) which uses reverse transcription and T7 RNA polymerase and

incorporates two primers to target its cycling scheme. NASBA can begin with either DNA or RNA and finish with either, and amplifies to 10^8 copies within 60 to 90 minutes. Alternatively, nucleic acid can be amplified by ligation activated transcription (LAT). LAT works from a single-stranded template with a single
5 primer that is partially single-stranded and partially double-stranded. Amplification is initiated by ligating a cDNA to the promoter oligonucleotide and within a few hours, amplification is 10^8 to 10^9 fold. Another amplification system useful in the method of the invention is the QB Replicase System. The QB replicase system can be utilized by attaching an RNA sequence called MDV-1
10 to RNA complementary to a DNA sequence of interest. Upon mixing with a sample, the hybrid RNA finds its complement among the specimen's mRNAs and binds, activating the replicase to copy the tag-along sequence of interest. Another nucleic acid amplification technique, ligase chain reaction (LCR), works by using two differently labeled halves of a sequence of interest which are
15 covalently bonded by ligase in the presence of the contiguous sequence in a sample, forming a new target. The repair chain reaction (RCR) nucleic acid amplification technique uses two complementary and target-specific oligonucleotide probe pairs, thermostable polymerase and ligase, and DNA nucleotides to geometrically amplify targeted sequences. A 2-base gap separates
20 the oligonucleotide probe pairs, and the RCR fills and joins the gap, mimicking DNA repair. Nucleic acid amplification by strand displacement activation (SDA) utilizes a short primer containing a recognition site for *hincII* with short overhang on the 5' end which binds to target DNA. A DNA polymerase fills in the part of the primer opposite the overhang with sulfur-containing adenine
25 analogs. *HincII* is added but only cuts the unmodified DNA strand. A DNA polymerase that lacks 5' exonuclease activity enters at the site of the nick and begins to polymerize, displacing the initial primer strand downstream and building a new one which serves as more primer. SDA produces greater than 10^7 -fold amplification in 2 hours at 37°C. Unlike PCR and LCR, SDA does not
30 require instrumented Temperature cycling.

Another method is a process for amplifying nucleic acid sequences from a DNA or RNA template which may be purified or may exist in a mixture of

nucleic acids. The resulting nucleic acid sequences may be exact copies of the template, or may be modified. The process has advantages over PCR in that it increases the fidelity of copying a specific nucleic acid sequence, and it allows one to more efficiently detect a particular point mutation in a single assay. A target nucleic acid is amplified enzymatically while avoiding strand displacement. Three primers are used. A first primer is complementary to the first end of the target. A second primer is complementary to the second end of the target. A third primer which is similar to the first end of the target and which is substantially complementary to at least a portion of the first primer such that when the third primer is hybridized to the first primer, the position of the third primer complementary to the base at the 5' end of the first primer contains a modification which substantially avoids strand displacement. This method is detailed in U.S. Patent 5,593,840 to Bhatnagar et al. 1997. Although PCR is the preferred method of amplification if the invention, these other methods can also be used to amplify the BRCA1 locus as described in the method of the invention.

The BRCA1^(omi) DNA coding sequences were obtained by end to end sequencing of the BRCA1 alleles of five subjects in the manner described above followed by analysis of the data obtained. The data obtained provided us with the opportunity to evaluate seven previously published polymorphisms and to affirm or correct where necessary, the frequency of occurrence of alternative codons.

GENE THERAPY

The coding sequences can be used for gene therapy.

A variety of methods are known for gene transfer, any of which might be available for use.

Direct injection of Recombinant DNA in vivo

1. Direct injection of "naked" DNA directly with a syringe and needle into a specific tissue, infused through a vascular bed, or transferred through a catheter into endothelial cells.

2. Direct injection of DNA that is contained in artificially generated lipid vesicles.

3. Direct injection of DNA conjugated to a targeting structure, such as an

antibody.

4. Direct injection by particle bombardment, where the DNA is coated onto gold particles and shot into the cells.

5 *Human Artificial Chromosomes*

This novel gene delivery approach involves the use of human chromosomes that have been striped down to contain only the essential components for replication and the genes desired for transfer.

10 *Receptor-Mediated Gene Transfer*

DNA is linked to a targeting molecule that will bind to specific cell-surface receptors, inducing endocytosis and transfer of the DNA into mammalian cells. One such technique uses poly-L-lysine to link asialoglycoprotein to DNA. An adenovirus is also added to the complex to disrupt the lysosomes and thus allow the DNA to avoid degradation and move to the nucleus. Infusion of these particles intravenously has resulted in gene transfer into hepatocytes.

RECOMBINANT VIRUS VECTORS

Several vectors are used in gene therapy. Among them are the Moloney Murine Leukemia Virus (MoMLV) Vectors, the adenovirus vectors, the adeno-Associated Virus (AAV) vectors, the herpes simplex virus (HSV) vectors, the poxvirus vectors, and human immunodeficiency virus (HIV) vectors,

GENE REPLACEMENT AND REPAIR

25 The ideal genetic manipulation for treatment of a genetic disease would be the actual replacement of the defective gene with a normal copy of the gene. Homologous recombination is the term used for switching out a section of DNA and replacing it with a new piece. By this technique, the defective gene can be replaced with a normal gene which expresses a functioning BRCA1 tumor growth inhibitor protein.

30 A complete description of gene therapy can also be found in "Gene Therapy A Primer For Physicians 2d Ed. by Kenneth W. Culver, M.D. Publ. Mary Ann

Liebert Inc. (1996). Two Gene Therapy Protocols for BRCA1 are approved by the Recombinant DNA Advisory Committee for Jeffrey T. Holt *et al.*. They are listed as 9602-148, and 9603-149 and are available from the NIH. The isolated BRCA1 gene can be synthesized or constructed from amplification products and inserted into a vector such as the LXS vector.

The BRCA1 amino acid and nucleic acid sequence may be used to make diagnostic probes and antibodies. Labeled diagnostic probes may be used by any hybridization method to determine the level of BRCA1 protein in serum or lysed cell suspension of a patient, or solid surface cell sample.

The BRCA1 amino acid sequence may be used to provide a level of protection for patients against risk of breast or ovarian cancer or to reduce the size of a tumor. Methods of making and extracting proteins are well known. Itakura *et al.* U.S. Patents 4,704,362, 5, 221, 619, and 5,583,013. BRCA1 has been shown to be secreted. Jensen, R.A. *et al. Nature Genetics* 12: 303-308 (1996).

EXAMPLE 1

Determination Of The Coding Sequence Of A BRCA1^(omi) Gene From Five Individuals

MATERIALS AND METHODS

Approximately 150 volunteers were screened in order to identify individuals with no cancer history in their immediate family (i.e. first and second degree relatives). Each person was asked to fill out a hereditary cancer prescreening questionnaire See TABLE I below. Five of these were randomly chosen for end-to-end sequencing of their BRCA1 gene. A first degree relative is a parent, sibling, or offspring. A second degree relative is an aunt, uncle, grandparent, grandchild, niece, nephew, or half-sibling.

TABLE I

Hereditary Cancer Pre-Screening Questionnaire

Part A: Answer the following questions about your family

1. To your knowledge, has anyone in your family been diagnosed with a very specific hereditary colon disease called Familial Adenomatous Polyposis (FAP)?
2. To your knowledge, have you or any aunt had breast cancer diagnosed before the age 35?
3. Have you had Inflammatory Bowel Disease, also called Crohn's Disease or Ulcerative Colitis, for more than 7 years?

Part B: Refer to the list of cancers below for your responses only to questions in Part B

Bladder Cancer	Lung Cancer	Pancreatic Cancer
Breast Cancer	Gastric Cancer	Prostate Cancer
Colon Cancer	Malignant Melanoma	Renal Cancer
Endometrial Cancer	Ovarian Cancer	Thyroid Cancer

4. Have your mother or father, your sisters or brothers or your children had any of the listed cancers?
5. Have there been diagnosed in your mother's brothers or sisters, or your mother's parents more than one of the cancers in the above list?
6. Have there been diagnosed in your father's brothers or sisters, or your father's parents more than one of the cancers in the above list?

Part C: Refer to the list of relatives below for responses only to questions in Part C

You	Your mother
Your sisters or brothers	Your mother's sisters or brothers (maternal aunts and uncles)
Your children	Your mother's parents (maternal grandparents)

7. Have there been diagnosed in these relatives 2 or more identical types of cancer?
Do not count "simple" skin cancer, also called basal cell or squamous cell skin cancer.
8. Is there a total of 4 or more of any cancers in the list of relatives above other than "simple" skin cancers?

Part D: Refer to the list of relatives below for responses only to questions in Part D.

You	Your father
Your sisters or brothers	Your father's sisters or brothers (paternal aunts and uncles)
Your children	Your father's parents (paternal grandparents)

9. Have there been diagnosed in these relatives 2 or more identical types of cancer?
Do not count "simple" skin cancer, also called basal cell or squamous cell skin cancer.
10. Is there a total of 4 or more of any cancers in the list of relatives above other than "simple" skin cancers?

Genomic DNA was isolated from white blood cells of five subjects selected from analysis of their answers to the questions above. Dideoxy sequence analysis was performed following polymerase chain reaction amplification.

All exons of the BRCA1 gene were subjected to direct dideoxy sequence analysis by asymmetric amplification using the polymerase chain reaction (PCR) to generate a single stranded product amplified from this DNA sample. Shuldiner, *et al.*, Handbook of Techniques in Endocrine Research, p. 457-486, DePablo, F., Scanes, C., eds., Academic Press, Inc., 1993. Fluorescent dye was attached for automated sequencing using the Taq Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing was performed in both forward and reverse directions on an Applied Biosystems, Inc. (ABI) automated Model 377® sequencer. The software used for analysis of the resulting data was Sequence Navigator® software purchased through ABI.

1. Polymerase Chain Reaction (PCR) Amplification

Genomic DNA (100 nanograms) extracted from white blood cells of five subjects. Each of the five samples was sequenced end to end. Each sample was amplified in a final volume of 25 microliters containing 1 microliter (100 nanograms) genomic DNA, 2.5 microliters 10X PCR buffer (100 mM Tris, pH 8.3, 500 mM KCl, 1.2 mM MgCl₂), 2.5 microliters 10X dNTP mix (2 mM each nucleotide), 2.5 microliters forward primer, 2.5 microliters reverse primer, and 1 microliter Taq polymerase (5 units), and 13 microliters of water.

The primers in Table II, below were used to carry out amplification of the various sections of the BRCA1 gene samples. The primers were synthesized on an DNA/RNA Model 394® Synthesizer.

TABLE II
BRCA1 PRIMERS AND SEQUENCING DATA

	EXON	SEQUENCE	SEQ.ID NO.	MER	Mg ⁺⁺	SIZE
5	EXON 2	2F 5' GAA GTT GTC ATT TTA TAA ACC TTT-3'	7	24	1.6	~275
		2R 5' TGT CTT TTC TTC CCT AGT ATG T-3'	8	22		
10	EXON 3	3F 5' TCC TGA CAC AGC AGA CAT TTA-3'	9	21	1.4	~375
		3R 5' TTG GAT TTT CGT TCT CAC TTA-3'	10	21		
	EXON 5	5F 5' CTC TTA AGG GCA GTT GTG AG-3'	11	20	1.2	~275
		5R 5' TTC CTA CTG TGG TTG CTT CC	12	20 ¹		
15	EXON 6	6/7F 5' CTT ATT TTA GTG TCC TTA AAA GG-3'	13	23	1.6	~250
		6R 5' TTT CAT GGA CAG CAC TTG AGT G-3'	14	22		
20	EXON 7	7F 5' CAC AAC AAA GAG CAT ACA TAG GG-3'	15	23	1.6	~275
		6/7R 5' TCG GGT TCA CTC TGT AGA AG-3'	16	20		
25	EXON 8	8F1 5' TTC TCT TCA GGA GGA AAA GCA-3'	17	21	1.2	~270
		8R1 5' GCT GGC TAC CAC AAA TAC AAA-3'	18	21		
25	EXON 9	9F 5' CCA CAG TAG ATG CTC AGT AAATA-3'	19	23	1.2	~250
		9R 5' TAG GAA AAT ACC AGC TTC ATA GA-3'	20	23		
	EXOM 10	10F 5' TGG TCA GCT TTC TGT AAT CG-3'	21	20	1.6	~250
		10R 5' GTA TCT ACC CAC TCT CTT CTT CAG-3'	22	24		
30	EXON 11A11AF	5' CCA CCT CCA AGG TGT ATC A-3'	23	19	1.2	372
	11AR	5' TGT TAT GTT GGC TCC TTG CT-3'	24	20		
35	EXON 11B11BF1	5' CAC TAA AGA CAG AAT GAA TCT A-3;	25	21	1.2	~400
	11BR1	5' GAA GAA CCA GAA TAT TCA TCT A-3'	26	21		
	EXON 11C11CF1	5' TGA TGG GGA GTC TGA ATC AA-3'	27	20	1.2	~400
	11CR1	5' TCT GCT TTC TTG ATA AAA TCC T-3'	28	22		
40	EXON 11D11DF1	5' AGC GTC CCC TCA CAA ATA AA-3'	29	20	1.2	~400
	11DR1	5' TCA AGC GCA TGA ATA TGC CT-3'	30	20		
	EXON 11E11EF	5' GTA TAA GCA ATA TGG AAC TCG A-3'	31	22	1.2	388
	11ER	5' TTA AGT TCA CTG GTA TTT GAA CA-3'	32	23		
45	EXON 11F11FF	5' GAC AGC GAT ACT TTC CCA GA-3'	33	20	1.2	382
	11FR	5' TGG AAC AAC CAT GAA TTA GTC-3'	34	21		
	EXON 11G11GF	5' GGA AGT TAG CAC TCT AGG GA-3'	35	20	1.2	423
50		11GR 5' GCA GTG ATA TTA ACT GTC TGT A-3'	36	22		

¹ M13 tailed

Thirty-five cycles were performed, each consisting of denaturing (95°C; 30 seconds), annealing (55°C; 1 minute), and extension (72°C; 90 seconds), except during the first cycle in which the denaturing time was increased to 5 minutes, and during the last cycle in which the extension time was increased to 5 minutes.

- 5 PCR products were purified using Qia-quick® PCR purification kits (Qiagen cat# 28104; Chatsworth, CA). Yield and purity of the PCR product determined spectrophotometrically at OD₂₆₀ on a Beckman DU 650 spectrophotometer.

2. Dideoxy Sequence Analysis

- 10 Fluorescent dye was attached to PCR products for automated sequencing using the Taq Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing was performed in both forward and reverse directions on an Applied Biosystems, Inc. (ABI) Foster City, CA., automated Model 377® sequencer. The software used for analysis of the resulting data was "Sequence Navigator® software" purchased through ABI.

3. RESULTS

- 15 Differences in the nucleic acids of the ten alleles from five individuals were found in seven locations on the gene. The changes and their positions are found on TABLE III, below.

TABLE III
PANEL TYPING

5	AMINO ACID CHANGE	NUCLEOTIDE					FREQUENCY
		CHANGE	1	2	3	4	
10	SER(SER) (694)	11E	C/C	C/T	C/T	T/T	0.4 C 0.6 T
	LEU(LEU) (771)	11F	T/T	C/T	C/T	C/C	0.4 T 0.6 C
15	PRO(LEU) (871)	11G	C/T	C/T	C/T	T/T	0.3 C 0.7 T
20	GLU(GLY) (1038)	11I	A/A	A/G	A/G	G/G	0.4 A 0.6 G
	LYS(ARG) (1183)	11J	A/A	A/G	A/G	G/G	0.4 A 0.6 G
25	SER(SER) (1436)	13	T/T	T/T	T/C	C/C	0.5 T 0.5 C
	SER(GLY) (1613)	16	A/A	A/G	A/G	G/G	0.4 A 0.6 G

Tables 3 and 4 depict one aspect of the invention, sets of at least two alternative codon pairs wherein the codon pairs occur in the following frequencies, respectively, in a population of individuals free of disease:

- at position 2201, AGC and AGT occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2430, TTG and CTG occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 2731, CCG and CTG occur at frequencies from about 25-35%, and from about 65-75%, respectively;
- at position 3232, GAA and GGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 3667, AAA and AGA occur at frequencies from about 35-45%, and from about 55-65%, respectively;
- at position 4427, TCT and TCC occur at frequencies from about 45-55%, and from about 45-55%, respectively; and
- at position 4956, AGT and GGT occur at frequencies from about 35-45%, and from about 55-65%, respectively.

The data show that for each of the samples. The BRCA1 gene is identical except in the region of seven polymorphisms. These polymorphic regions, together with their locations, the amino acid groups of each codon, the frequency of their occurrence and the amino acid coded for by each codon are found in TABLE IV below.

TABLE IV
CODON AND BASE CHANGES IN SEVEN POLYMORPHIC SITES OF BRCA1 GENE

SAMPLE NAME	BASE CHANGE	POSITION nt/aa	EXON	CODON CHANGE	AA CHANGE	PUBLISHED FREQUENCY ²	FREQUENCY IN THIS STUDY
2,3,4,5	C-T	2201/694	11E	AGC(AGT)	SER-SER	UNPUBLISHED	C=40%
2,3,4,5	T-C	2430/771	11F	TTG(CTG)	LEU-LEU	T=67% ¹³	T=40%
1,2,3,4,5	C-T	2731/871	11G	CCG(CTG)	PRO-LEU	C=34% ¹²	C=30%

	2,3,4,5	A-G	3232/1038	11I	GAA(GGA)	GLU-GLY	A=67% ¹³	A=40%
	2,3,4,5	A-G	3667/1183	11J	AAA(AGA)	LYS-ARG	A=68% ¹²	A=40%
5	3,4,5	T-C	4427/1436	13	TCT(TCC)	SER-SER	T=67% ¹²	T=50%
	2,3,4,5	A-G	4956/1613	16	AGT(GGT)	SER-GLY	A=67% ¹²	A=40%

²Reference numbers correspond to the Table of References below.

EXAMPLE 2

Determination Of A Individual Using BRCA1^(OMI) And The Seven Polymorphisms For Reference

A person skilled in the art of genetic susceptibility testing will find the present invention useful for:

a) identifying individuals having a BRCA1 gene, who are therefore have no elevated genetic susceptibility to breast or ovarian cancer from a BRCA1 mutation;

b) avoiding misinterpretation of polymorphisms found in the

BRCA1 gene;

Sequencing is carried out as in EXAMPLE 1 using a blood sample from the patient in question. However, a BRCA1^(omi) sequence is used for reference and the polymorphic sites are compared to the nucleic acid sequences listed above for codons at each polymorphic site. A sample is one which compares to a BRCA1^(omi) sequence and contains one of the base variations which occur at each of the polymorphic sites. The codons which occur at each of the polymorphic sites are paired here reference.

- AGC and AGT at position 2201,
- TTG and CTG at position 2430,
- CCG and CTG at position 2731,
- GAA and GGA at position 3232,
- AAA and AGA at position 3667,
- TCT and TCC at position 4427, and
- AGT and GGT at position 4956.

The availability of these polymorphic pairs provides added assurance that one skilled in the art can correctly interpret the polymorphic variations without mistaking a variation for a mutation.

Exon 11 of the BRCA1 gene is subjected to direct dideoxy sequence analysis by asymmetric amplification using the polymerase chain reaction (PCR) to generate a single stranded product amplified from this DNA sample. Shuldiner, *et al.*, Handbook of Techniques in Endocrine Research, p. 457-486, DePablo, F., Scanes, C., eds., Academic Press, Inc., 1993. Fluorescent dye is attached for automated sequencing using the Taq Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in

both forward and reverse directions on an Applied Biosystems, Inc. (ABI) automated Model 377® sequencer. The software used for analysis of the resulting data is "Sequence Navigator® software" purchased through ABI.

5 1. Polymerase Chain Reaction (PCR) Amplification

Genomic DNA (100 nanograms) extracted from white blood cells of the subject is amplified in a final volume of 25 microliters containing 1 microliter (100 nanograms) genomic DNA, 2.5 microliters 10X PCR buffer (100 mM Tris, pH 8.3, 500 mM KCl, 1.2 mM MgCl₂), 2.5 microliters 10X dNTP mix (2 mM each nucleotide), 2.5 microliters
10 forward primer (BRCA1-11K-F, 10 micromolar solution), 2.5 microliters reverse primer (BRCA1-11K-R, 10 micromolar solution), and 1 microliter Taq polymerase (5 units), and 13 microliters of water.

The PCR primers used to amplify a patient's sample BRCA1 gene are listed in Table II. The primers were synthesized on an DNA/RNA Model 394® Synthesizer. Thirty-five
15 cycles of amplification are performed, each consisting of denaturing (95°C; 30 seconds), annealing (55°C; 1 minute), and extension (72°C; 90 seconds), except during the first cycle in which the denaturing time is increased to 5 minutes, and during the last cycle in which the extension time is increased to 5 minutes.

PCR products are purified using Qia-quick® PCR purification kits (Qiagen, cat# 28104; Chatsworth, CA). Yield and purity of the PCR product determined
20 spectrophotometrically at OD₂₆₀ on a Beckman DU 650 spectrophotometer.

2. Dideoxy Sequence Analysis

Fluorescent dye is attached to PCR products for automated sequencing using the Taq
25 Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in both forward and reverse directions on an Applied Biosystems, Inc. (ABI) Foster City, CA., automated Model 377® sequencer. The software used for analysis of the resulting data is "Sequence Navigator® software" purchased through ABI. The BRCA1(omi1) SEQ. ID. NO.:1 sequence is entered into the Sequence Navigator® software as the Standard for
30 comparison. The Sequence Navigator® software compares the sample sequence to the BRCA1(omi1) SEQ. ID. NO.:1 standard, base by base. The Sequence Navigator® software

highlights all differences between the BRCA1^(omi1) SEQ. ID. NO.:1 DNA sequence and the patient's sample sequence.

A first technologist checks the computerized results by comparing visually the BRCA1^(omi1) SEQ. ID. NO.:1 standard against the patient's sample, and again highlights any differences between the standard and the sample. The first primary technologist then interprets the sequence variations at each position along the sequence. Chromatograms from each sequence variation are generated by the Sequence Navigator[®] software and printed on a color printer. The peaks are interpreted by the first primary technologist and a second primary technologist. A secondary technologist then reviews the chromatograms. The results are finally interpreted by a geneticist. In each instance, a variation is compared to known polymorphisms for position and base change. If the sample BRCA1 sequence matches the BRCA1^(omi1) SEQ. ID. NO.:1 standard, with only variations within the known list of polymorphisms, it is interpreted as a gene sequence.

EXAMPLE 3

DETERMINING THE ABSENCE OF A MUTATION IN THE BRCA1 GENE USING BRCA1^(omi1) AND SEVEN POLYMORPHISMS FOR REFERENCE

A person skilled in the art of genetic susceptibility testing will find the present invention useful for determining the presence of a known or previously unknown mutation in the BRCA1 gene. A list of mutations of BRCA1 is publicly available in the Breast Cancer Information Core at:

http://www.nchgr.nih.gov/dir/lab_transfer/bic. This data site became publicly available on November 1, 1995. Friend, S. *et al. Nature Genetics* 11:238, (1995).

Sequencing is carried out as in EXAMPLE 1 using a blood sample from the patient in question. However, a BRCA1^(omi) sequence is used for reference and polymorphic sites are compared to the nucleic acid sequences listed above for codons at each polymorphic site. A sample is one which compares to the BRCA1^(omi2) SEQ. ID. NO.: 3 sequence and contains one of the base variations which occur at each of the polymorphic sites. The codons which occur at each of the polymorphic sites are paired here reference.

- AGC and AGT at position 2201,
- TTG and CTG at position 2430,

- CCG and CTG at position 2731,
- GAA and GGA at position 3232,
- AAA and AGA at position 3667,
- TCT and TCC at position 4427, and
- 5 • AGT and GGT at position 4956.

The availability of these polymorphic pairs provides added assurance that one skilled in the art can correctly interpret the polymorphic variations without mistaking a variation for a mutation.

10 Exon 11 of the BRCA1 gene is subjected to direct dideoxy sequence analysis by asymmetric amplification using the polymerase chain reaction (PCR) to generate a single stranded product amplified from this DNA sample. Shuldiner, *et al.*, Handbook of Techniques in Endocrine Research, p. 457-486, DePablo, F., Scanes, C., eds., Academic Press, Inc., 1993. Fluorescent dye is attached for automated sequencing using the Taq Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in
15 both forward and reverse directions on an Applied Biosystems, Inc. (ABI) automated Model 377® sequencer. The software used for analysis of the resulting data is "Sequence Navigator® software" purchased through ABI.

1. Polymerase Chain Reaction (PCR) Amplification

20 Genomic DNA (100 nanograms) extracted from white blood cells of the subject is amplified in a final volume of 25 microliters containing 1 microliter (100 nanograms) genomic DNA, 2.5 microliters 10X PCR buffer (100 mM Tris, pH 8.3, 500 mM KCl, 1.2 mM MgCl₂), 2.5 microliters 10X dNTP mix (2 mM each nucleotide), 2.5 microliters forward primer (BRCA1-11K-F, 10 micromolar solution), 2.5 microliters reverse primer
25 (BRCA1-11K-R, 10 micromolar solution), and 1 microliter Taq polymerase (5 units), and 13 microliters of water.

The PCR primers used to amplify a patient's sample BRCA1 gene are listed in Table II. The primers were synthesized on an DNA/RNA Model 394® Synthesizer. Thirty-five cycles of amplification are performed, each consisting of denaturing (95°C; 30
30 seconds), annealing (55°C; 1 minute), and extension (72°C; 90 seconds), except during the first cycle in which the denaturing time is increased to 5 minutes, and during the

last cycle in which the extension time is increased to 5 minutes.

5 PCR products are purified using Qia-quick® PCR purification kits (Qiagen, cat# 28104; Chatsworth, CA). Yield and purity of the PCR product determined spectrophotometrically at OD₂₆₀ on a Beckman DU 650 spectrophotometer.

2. Dideoxy Sequence Analysis

10 Fluorescent dye is attached to PCR products for automated sequencing using the Taq Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in both forward and reverse directions on an Applied Biosystems, Inc. (ABI) Foster City, CA., automated Model 377® sequencer. The software used for analysis of the resulting data is "Sequence Navigator® software" purchased through ABI. The BRCA1(omi2) SEQ. ID. NO.: 3 sequence is entered into the Sequence Navigator® software as the Standard for comparison. The Sequence Navigator® software compares the sample sequence to
15 the BRCA1(omi2) SEQ. ID. NO.: 3 standard, base by base. The Sequence Navigator® software highlights all differences between the BRCA1(omi2) SEQ. ID. NO.: 3 DNA sequence and the patient's sample sequence.

A first technologist checks the computerized results by comparing visually the BRCA1(omi2) SEQ. ID. NO.: 3 standard against the patient's sample, and again highlights
20 any differences between the standard and the sample. The first primary technologist then interprets the sequence variations at each position along the sequence. Chromatograms from each sequence variation are generated by the Sequence Navigator® software and printed on a color printer. The peaks are interpreted by the first primary technologist and also by a second primary technologist. A secondary
25 technologist then reviews the chromatograms. The results are finally interpreted by a geneticist. In each instance, a variation is compared to known polymorphisms for position and base change. If the sample BRCA1 sequence matches the BRCA1(omi2) SEQ. ID. NO.: 3 standard, with only variations within the known list of polymorphisms, it is interpreted as a gene sequence.

30

EXAMPLE 4

DETERMINING THE PRESENCE OF A MUTATION IN THE BRCA1 GENE USING BRCA1^(omi) AND SEVEN POLYMORPHISMS FOR REFERENCE

A person skilled in the art of genetic susceptibility testing will find the present invention useful for determining the presence of a known or previously unknown mutation in the BRCA1 gene. A list of mutations of BRCA1 is publicly available in the Breast Cancer Information Core at:

http://www.nchgr.nih.gov/dir/lab_transfer/bic. This data site became publicly available on November 1, 1995. Friend, S. *et al.* *Nature Genetics* 11:238, (1995). In this example, a mutation in exon 11 is characterized by amplifying the region of the mutation with a primer which matches the region of the mutation.

Exon 11 of the BRCA1 gene is subjected to direct dideoxy sequence analysis by asymmetric amplification using the polymerase chain reaction (PCR) to generate a single stranded product amplified from this DNA sample. Shuldiner, *et al.*, Handbook of Techniques in Endocrine Research, p. 457-486, DePablo, F., Scanes, C., eds., Academic Press, Inc., 1993. Fluorescent dye is attached for automated sequencing using the Taq Dye Terminator[®] Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in both forward and reverse directions on an Applied Biosystems, Inc. (ABI) automated Model 377[®] sequencer. The software used for analysis of the resulting data is "Sequence Navigator[®] software" purchased through ABI.

1. Polymerase Chain Reaction (PCR) Amplification

Genomic DNA (100 nanograms) extracted from white blood cells of the subject is amplified in a final volume of 25 microliters containing 1 microliter (100 nanograms) genomic DNA, 2.5 microliters 10X PCR buffer (100 mM Tris, pH 8.3, 500 mM KCl, 1.2 mM MgCl₂), 2.5 microliters 10X dNTP mix (2 mM each nucleotide), 2.5 microliters forward primer (BRCA1-11K-F, 10 micromolar solution), 2.5 microliters reverse primer (BRCA1-11K-R, 10 micromolar solution), and 1 microliter Taq polymerase (5 units), and 13 microliters of water.

The PCR primers used to amplify segment K of exon 11 (where the mutation is found) are as follows:

BRCA1-11K-F: 5'-GCA AAA GCG TCC AGA AAG GA-3' SEQ ID NO:69

BRCA1-11K-R: 5'-AGT CTT CCA ATT CAC TGC AC-3' SEQ ID NO:70

The primers are synthesized on an DNA/RNA Model 394® Synthesizer.

5 Thirty-five cycles are performed, each consisting of denaturing (95°C; 30 seconds),
annealing (55°C; 1 minute), and extension (72°C; 90 seconds), except during the first
cycle in which the denaturing time is increased to 5 minutes, and during the last cycle
in which the extension time is increased to 5 minutes.

10 PCR products are purified using Qia-quick® PCR purification kits (Qiagen, cat# 28104;
Chatsworth, CA). Yield and purity of the PCR product determined
spectrophotometrically at OD₂₆₀ on a Beckman DU 650 spectrophotometer.

2. Dideoxy Sequence Analysis

15 Fluorescent dye is attached to PCR products for automated sequencing using the Taq
Dye Terminator® Kit (Perkin-Elmer cat# 401628). DNA sequencing is performed in
both forward and reverse directions on an Applied Biosystems, Inc. (ABI) Foster City,
CA., automated Model 377® sequencer. The software used for analysis of the resulting
data is "Sequence Navigator® software" purchased through ABI. The BRCA1^(omi2) SEQ.
ID. NO.: 3 sequence is entered into the Sequence Navigator® software as the Standard
for comparison. The Sequence Navigator® software compares the sample sequence to
20 the BRCA1^(omi2) SEQ. ID. NO.: 3 standard, base by base. The Sequence Navigator®
software highlights all differences between the BRCA1^(omi2) SEQ. ID. NO.: 3 DNA
sequence and the patient's sample sequence.

A first technologist checks the computerized results by comparing visually the
BRCA1^(omi2) SEQ. ID. NO.: 3 standard against the patient's sample, and again highlights
25 any differences between the standard and the sample. The first primary technologist
then interprets the sequence variations at each position along the sequence.
Chromatograms from each sequence variation are generated by the Sequence
Navigator® software and printed on a color printer. The peaks are interpreted by the
first primary technologist and a second primary technologist. A secondary technologist
30 then reviews the chromatograms. The results are finally interpreted by a geneticist. In
each instance, a variation is compared to known polymorphisms for position and base

change. Mutations are noted by the length of non-matching variation. Such a lengthy mismatch pattern occurs with deletions and substitutions.

3. Result

Using the above PCR amplification and standard fluorescent sequencing technology, The 3888delGA mutation may be found. The 3888delGA mutation The BRCA1 gene lies in segment "K" of exon 11. The DNA sequence results demonstrate the presence of a two base pair deletion at nucleotides 3888 and 3889 of the published BRCA1^(omi) sequence. This mutation interrupts the reading frame of the BRCA1 transcript, resulting in the appearance of an in-frame terminator (TAG) at codon position 1265. This mutation is, therefore, predicted to result in a truncated, and most likely, non-functional protein. The formal name of the mutation will be 3888delGA. This mutation is named in accordance with the suggested nomenclature for naming mutations, Baudet, A *et al.*, *Human Mutation* 2:245-248, (1993).

EXAMPLE 5

USE OF THE BRCA1^(omi1) GENE THERAPY

The growth of ovarian, breast or prostate cancer can be arrested by increasing the expression of the BRCA1 gene where inadequate expression of that gene is responsible for hereditary ovarian, breast and prostate cancer. It has been demonstrated that transfection of BRCA1 into cancer cells inhibits their growth and reduces tumorigenesis. Gene therapy is performed on a patient to reduce the size of a tumor. The LXSXN vector is transformed with any of the BRCA1^(omi1) SEQ. ID. NO.:1, BRCA1^(omi2) SEQ. ID. NO.:3, or BRCA1^(omi3) SEQ. ID. NO.:5 coding region.

Vector

The LXSXN vector is transformed with wildtype BRCA1^(omi1) SEQ. ID. NO.:1 coding sequence. The LXSXN-BRCA1^(omi1) retroviral expression vector is constructed by cloning a *Sal*I-linked BRCA1^(omi1) cDNA (nucleotides 1-5711) into the *Xho*I site of the vector LXSXN. Constructs are confirmed by DNA sequencing. Holt *et al.* *Nature Genetics* 12: 298-302 (1996).

Retroviral vectors are manufactured from viral producer cells using serum free and phenol-red free conditions and tested for sterility, absence of specific pathogens, and absence of replication-competent retrovirus by standard assays. Retrovirus is stored frozen in aliquots which have been tested.

5 Patients receive a complete physical exam, blood, and urine tests to determine overall health. They may also have a chest X-ray, electrocardiogram, and appropriate radiologic procedures to assess tumor stage.

10 Patients with metastatic ovarian cancer are treated with retroviral gene therapy by infusion of recombinant LXS_N-BRCA1^(omi1) retroviral vectors into peritoneal sites containing tumor, between 10⁹ and 10¹⁰ viral particles per dose. Blood samples are drawn each day and tested for the presence of retroviral vector by sensitive polymerase chain reaction (PCR)-based assays. The fluid which is removed is analyzed to determine:

15 1. The percentage of cancer cells which are taking up the recombinant LXS_N-BRCA1^(omi1) retroviral vector combination. Successful transfer of BRCA1 gene into cancer cells is shown by both RT-PCR analysis and *in situ* hybridization.

RT-PCR is performed with by the method of Thompson *et al. Nature Genetics* 9: 444-450 (1995), using primers derived from BRCA1^(omi1) SEQ. ID. NO.:1. Cell lysates are
20 prepared and immunoblotting is performed by the method of Jensen *et al. Nature Genetics* 12: 303-308 1996) and Jensen *et al. Biochemistry* 31: 10887-10892 (1992).

25 2. Presence of programmed cell death using ApoTAG® *in situ* apoptosis detection kit (Oncor, Inc., Gaithersburg, Maryland) and DNA analysis.

3. Measurement of BRCA I gene expression by slide immunofluorescence or western blot.

Patients with measurable disease are also evaluated for a clinical response to LXS_N-BRCAI, especially those that do not undergo a palliative intervention immediately after
30 retroviral vector therapy. Fluid cytology, abdominal girth, CT scans of the abdomen, and local symptoms are followed.

For other sites of disease, conventional response criteria are used as follows:

1. Complete Response (CR), complete disappearance of all measurable lesions and of all signs and symptoms of disease for at least 4 weeks.
2. Partial Response (PR), decrease of at least 50% of the sum of the products of the 2 largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. To be considered a PR, no new lesions should have appeared during this period and none should have increased in size.
3. Stable Disease, less than 25% change in tumor volume from previous evaluations.
4. Progressive Disease, greater than 25% increase in tumor measurements from prior evaluations.

The number of doses depends upon the response to treatment.

For further information related to this gene therapy approach see in "BRCA1 Retroviral Gene Therapy for Ovarian Cancer" a Human Gene Transfer Protocol: NIH ORDA Registration #: 9603-149 Jeffrey Holt, JT, M.D. and Carlos L. Arteaga, M.D.

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- 5 18. Jensen, RA *et al.*, *Nature Genetics* 12:303-308 (1996).
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21. Holt, JT, and C. Arteaga, Gene Therapy Protocol ORDA #: 9603-149 ORDA approved Protocol for BRCA1 Gene Therapy .

10

"Breast and Ovarian cancer" is understood by those skilled in the art to include breast and ovarian cancer in women and also breast and prostate cancer in men. BRCA1 is associated genetic susceptibility to inherited breast and ovarian cancer in women and also breast and prostate cancer in men. Therefore, claims in this document which recite breast and/or ovarian cancer refer to breast, ovarian and prostate cancers in men and women. Although the invention has been described with reference to the presently preferred embodiments, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: A Sequence of the Human BRCA1 Gene

(iii) NUMBER OF SEQUENCES: 78

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(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: to be assigned
(B) FILING DATE: herewith
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

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(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 301-527-2051

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5711 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

(A) CHROMOSOME/SEGMENT: 17

(B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AGCTCGCTGA	GACTTCCTGG	ACCCCGCACC	AGGCTGTGGG	GTTTCTCAGA	TAACTGGGCC	60
CCTGCGCTCA	GGAGGCCTTC	ACCCTCTGCT	CTGGGTAAAG	TTCATTGGAA	CAGAAAGAAA	120
TGGATTTATC	TGCTCTTCGC	GTTGAAGAAG	TACAAAATGT	CATTAATGCT	ATGCAGAAAA	180
TCTTAGAGTG	TCCCATCTGT	CTGGAGTTGA	TCAAGGAACC	TGTCTCCACA	AAGTGTGACC	240
ACATATTTTG	CAAATTTTGC	ATGCTGAAAC	TTCTCAACCA	GAAGAAAGGG	CCTTCACAGT	300

GTCCTTTATG	TAAGAATGAT	ATAACCAAAA	GGAGCCTACA	AGAAAGTACG	AGATTTAGTC	360
AACTTGTTGA	AGAGCTATTG	AAAATCATTT	GTGCTTTTCA	GCTTGACACA	GGTTTGGAGT	420
ATGCAAACAG	CTATAATTTT	GCAAAAAAGG	AAAATAACTC	TCCTGAACAT	CTAAAAGATG	480
AAGTTTCTAT	CATCCAAAGT	ATGGGCTACA	GAAACCGTGC	CAAAGACTT	CTACAGAGTG	540
AACCCGAAAA	TCCTTCCTTG	CAGGAAACCA	GTCTCAGTGT	CCAACCTCTCT	AACCTTGGA	600
CTGTGAGAAC	TCTGAGGACA	AAGCAGCGGA	TACAACCTCA	AAAGACGTCT	GTCTACATTG	660
AATTGGGATC	TGATTCTTCT	GAAGATACCG	TTAATAAGGC	AACTTATTGC	AGTGTGGGAG	720
ATCAAGAATT	GTTACAAATC	ACCCCTCAAG	GAACCAGGGA	TGAAATCAGT	TTGGATTCTG	780
CAAAAAAGGC	TGCTTGTGAA	TTTTCTGAGA	CGGATGTAAC	AAATACTGAA	CATCATCAAC	840
CCAGTAATAA	TGATTTGAAC	ACCACTGAGA	AGCGTGCAGC	TGAGAGGCAT	CCAGAAAAGT	900
ATCAGGGTAG	TTCTGTTTCA	AACTTGCATG	TGGAGCCATG	TGGCACAAAT	ACTCATGCCA	960
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CAGAGAATCC	TAGAGATACT	GAAGATGTTC	CTTGGATAAC	ACTAAATAGC	AGCATTGAGA	1260
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AAAGATCTGT	AGAGAGTAGC	AGTATTTTAC	TGGTACCTGG	TACTGATTAT	GGCACTCAGG	2460
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ACGAAACTGG	ACTCATTACT	CCAAATAAAC	ATGGACTTTT	ACAAAACCCA	TATCGTATAC	3060
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AAGAGCTTCC	CTGCTTCCAA	CACTTGTTAT	TTGGTAAAGT	AAACAATATA	CCTTCTCAGT	3840
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ATACTGCTGG	GTATAATGCA	ATGGAAGAAA	GTGTGAGCAG	GGAGAAGCCA	GAATTGACAG	5040
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AGTCTATTAA	AGAAAGAAAA	ATGCTGAATG	AGCATGATTT	TGAAGTCAGA	GGAGATGTGG	5340
TCAATGGAAG	AAACCACCAA	GGTCCAAAGC	GAGCAAGAGA	ATCCCAGGAC	AGAAAGATCT	5400
TCAGGGGGCT	AGAAATCTGT	TGCTATGGGC	CCTTCACCAA	CATGCCCCACA	GATCAACTGG	5460
AATGGATGGT	ACAGCTGTGT	GGTGCTTCTG	TGGTGAAGGA	GCTTTCATCA	TTCACCCTTG	5520
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TCCATGCAAT	TGGGCAGATG	TGTGAGGCAC	CTGTGGTGAC	CCGAGAGTGG	GTGTTGGACA	5640
GTGTAGCACT	CTACCAGTGC	CAGGAGCTGG	ACACCTACCT	GATACCCCAG	ATCCCCCACA	5700
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42) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1863 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

- (A) CHROMOSOME/SEGMENT: 17
- (B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met	Asp	Leu	Ser	Ala	Leu	Arg	Val	Glu	Glu	Val	Gln	Asn	Val	Ile	Asn			
1				5					10					15				
Ala	Met	Gln	Lys	Ile	Leu	Glu	Cys	Pro	Ile	Cys	Leu	Glu	Leu	Ile	Lys			
			20					25					30					
Glu	Pro	Val	Ser	Thr	Lys	Cys	Asp	His	Ile	Phe	Cys	Lys	Phe	Cys	Met			
		35					40					45						
Leu	Lys	Leu	Leu	Asn	Gln	Lys	Lys	Gly	Pro	Ser	Gln	Cys	Pro	Leu	Cys			
	50					55					60							
Lys	Asn	Asp	Ile	Thr	Lys	Arg	Ser	Leu	Gln	Glu	Ser	Thr	Arg	Phe	Ser			
65					70					75					80			
Gln	Leu	Val	Glu	Glu	Leu	Leu	Lys	Ile	Ile	Cys	Ala	Phe	Gln	Leu	Asp			
			85					90					95					
Thr	Gly	Leu	Glu	Tyr	Ala	Asn	Ser	Tyr	Asn	Phe	Ala	Lys	Lys	Glu	Asn			
		100						105					110					
Asn	Ser	Pro	Glu	His	Leu	Lys	Asp	Glu	Val	Ser	Ile	Ile	Gln	Ser	Met			
		115					120					125						
Gly	Tyr	Arg	Asn	Arg	Ala	Lys	Arg	Leu	Leu	Gln	Ser	Glu	Pro	Glu	Asn			
	130					135					140							
Pro	Ser	Leu	Gln	Glu	Thr	Ser	Leu	Ser	Val	Gln	Leu	Ser	Asn	Leu	Gly			
145				150						155					160			
Thr	Val	Arg	Thr	Leu	Arg	Thr	Lys	Gln	Arg	Ile	Gln	Pro	Gln	Lys	Thr			
			165					170					175					
Ser	Val	Tyr	Ile	Glu	Leu	Gly	Ser	Asp	Ser	Ser	Glu	Asp	Thr	Val	Asn			
		180						185				190						

Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
 195 200 205

Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
 210 215 220

Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
 225 230 235 240

Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
 245 250 255

His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
 260 265 270

Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
 275 280 285

Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
 290 295 300

Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
 305 310 315 320

Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
 325 330 335

Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
 340 345 350

Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
 355 360 365

Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
 370 375 380

Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
 385 390 395 400

Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu

				405					410					415		
Asn	Glu	Val	Asp	Glu	Tyr	Ser	Gly	Ser	Ser	Glu	Lys	Ile	Asp	Leu	Leu	
			420					425					430			
Ala	Ser	Asp	Pro	His	Glu	Ala	Leu	Ile	Cys	Lys	Ser	Glu	Arg	Val	His	
		435					440					445				
Ser	Lys	Ser	Val	Glu	Ser	Asn	Ile	Glu	Asp	Lys	Ile	Phe	Gly	Lys	Thr	
	450					455					460					
Tyr	Arg	Lys	Lys	Ala	Ser	Leu	Pro	Asn	Leu	Ser	His	Val	Thr	Glu	Asn	
465					470				475					480		
Leu	Ile	Ile	Gly	Ala	Phe	Val	Thr	Glu	Pro	Gln	Ile	Ile	Gln	Glu	Arg	
			485						490					495		
Pro	Leu	Thr	Asn	Lys	Leu	Lys	Arg	Lys	Arg	Arg	Pro	Thr	Ser	Gly	Leu	
			500					505					510			
His	Pro	Glu	Asp	Phe	Ile	Lys	Lys	Ala	Asp	Leu	Ala	Val	Gln	Lys	Thr	
		515					520					525				
Pro	Glu	Met	Ile	Asn	Gln	Gly	Thr	Asn	Gln	Thr	Glu	Gln	Asn	Gly	Gln	
	530					535				540						
Val	Met	Asn	Ile	Thr	Asn	Ser	Gly	His	Glu	Asn	Lys	Thr	Lys	Gly	Asp	
545					550				555					560		
Ser	Ile	Gln	Asn	Glu	Lys	Asn	Pro	Asn	Pro	Ile	Glu	Ser	Leu	Glu	Lys	
			565					570					575			
Glu	Ser	Ala	Phe	Lys	Thr	Lys	Ala	Glu	Pro	Ile	Ser	Ser	Ser	Ile	Ser	
		580					585						590			
Asn	Met	Glu	Leu	Glu	Leu	Asn	Ile	His	Asn	Ser	Lys	Ala	Pro	Lys	Lys	
	595					600					605					
Asn	Arg	Leu	Arg	Arg	Lys	Ser	Ser	Thr	Arg	His	Ile	His	Ala	Leu	Glu	
	610					615				620						

Leu	Val	Val	Ser	Arg	Asn	Leu	Ser	Pro	Pro	Asn	Cys	Thr	Glu	Leu	Gln	625			630			635					640
Ile	Asp	Ser	Cys	Ser	Ser	Ser	Glu	Glu	Ile	Lys	Lys	Lys	Lys	Tyr	Asn				645			650				655	
Gln	Met	Pro	Val	Arg	His	Ser	Arg	Asn	Leu	Gln	Leu	Met	Glu	Gly	Lys				660			665				670	
Glu	Pro	Ala	Thr	Gly	Ala	Lys	Lys	Ser	Asn	Lys	Pro	Asn	Glu	Gln	Thr				675			680				685	
Ser	Lys	Arg	His	Asp	Ser	Asp	Thr	Phe	Pro	Glu	Leu	Lys	Leu	Thr	Asn				690			695				700	
Ala	Pro	Gly	Ser	Phe	Thr	Lys	Cys	Ser	Asn	Thr	Ser	Glu	Leu	Lys	Glu	705			710			715				720	
Phe	Val	Asn	Pro	Ser	Leu	Pro	Arg	Glu	Glu	Lys	Glu	Glu	Lys	Leu	Glu				725			730				735	
Thr	Val	Lys	Val	Ser	Asn	Asn	Ala	Glu	Asp	Pro	Lys	Asp	Leu	Met	Leu				740			745				750	
Ser	Gly	Glu	Arg	Val	Leu	Gln	Thr	Glu	Arg	Ser	Val	Glu	Ser	Ser	Ser				755			760				765	
Ile	Ser	Leu	Val	Pro	Gly	Thr	Asp	Tyr	Gly	Thr	Gln	Glu	Ser	Ile	Ser				770			775				780	
Leu	Leu	Glu	Val	Ser	Thr	Leu	Gly	Lys	Ala	Lys	Thr	Glu	Pro	Asn	Lys	785			790			795				800	
Cys	Val	Ser	Gln	Cys	Ala	Ala	Phe	Glu	Asn	Pro	Lys	Gly	Leu	Ile	His				805			810				815	
Gly	Cys	Ser	Lys	Asp	Asn	Arg	Asn	Asp	Thr	Glu	Gly	Phe	Lys	Tyr	Pro				820			825				830	
Leu	Gly	His	Glu	Val	Asn	His	Ser	Arg	Glu	Thr	Ser	Ile	Glu	Met	Glu												

835		840		845
Glu Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser				
850		855		860
Lys Arg Gln Ser Phe Ala Leu Phe Ser Asn Pro Gly Asn Ala Glu Glu				
865		870		875
				880
Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser				
		885		890
				895
Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys				
		900		905
				910
Asn Glu Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly				
		915		920
				925
Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys				
		930		935
				940
Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly				
945		950		955
				960
Asn Glu Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn				
		965		970
				975
Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr				
		980		985
				990
Lys Cys Lys Lys Asn Leu Leu Glu Glu Asn Phe Glu Glu His Ser Met				
		995		1000
				1005
Ser Pro Glu Arg Glu Met Gly Asn Glu Asn Ile Pro Ser Thr Val Ser				
		1010		1015
				1020
Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Gly Ala Ser				
1025		1030		1035
				1040
Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser				
		1045		1050
				1055

Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Glu Leu
 1060 1065 1070

Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
 1075 1080 1085

Leu Gln Pro Glu Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
 1090 1095 1100

His Pro Glu Ile Lys Lys Gln Glu Tyr Glu Glu Val Val Gln Thr Val
 1105 1110 1115 1120

Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
 1125 1130 1135

Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
 1140 1145 1150

Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
 1155 1160 1165

Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Arg Gly
 1170 1175 1180

Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
 1185 1190 1195 1200

Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
 1205 1210 1215

Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly
 1220 1225 1230

Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala
 1235 1240 1245

Thr Glu Cys Leu Ser Lys Asn Thr Glu Glu Asn Leu Leu Ser Leu Lys
 1250 1255 1260

Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser
 1265 1270 1275 1280

Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe
1285 1290 1295

Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr
1300 1305 1310

Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser
1315 1320 1325

Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp
1330 1335 1340

Glu Glu Arg Gly Thr Gly Leu Glu Glu Asn Asn Gln Glu Glu Gln Ser
1345 1350 1355 1360

Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Glu Ser Glu Thr
1365 1370 1375

Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
1380 1385 1390

Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
1395 1400 1405

Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
1410 1415 1420

Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu
1425 1430 1435 1440

Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
1445 1450 1455

Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
1460 1465 1470

Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
1475 1480 1485

Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
 1490. 1495 1500
 Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
 1505 1510 1515 1520
 Asn Tyr Pro Ser Gln Glu Glu Leu Ile Lys Val Val Asp Val Glu Glu
 1525 1530 1535
 Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
 1540 1545 1550
 Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
 1555 1560 1565
 Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Glu Asp Arg Ala
 1570 1575 1580
 Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu
 1585 1590 1595 1600
 Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Gly Pro Ala Ala
 1605 1610 1615
 Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val
 1620 1625 1630
 Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys
 1635 1640 1645
 Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu
 1650 1655 1660
 Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
 1665 1670 1675 1680
 Thr Glu Glu Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val
 1685 1690 1695
 Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
 1700 1705 1710

Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
1715 1720 1725

Leu Asn Glu His Asp Phe Glu Val Arg Gly Asp Val Val Asn Gly Arg
1730 1735 1740

Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile
1745 1750 1755 1760

Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
1765 1770 1775

Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
1780 1785 1790

Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
1795 1800 1805

Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
1810 1815 1820

Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
1825 1830 1835 1840

Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
1845 1850 1855

Gln Ile Pro His Ser His Tyr
1860

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5711 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

(A) CHROMOSOME/SEGMENT: 17

(B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGCTCGCTGA	GACTTCCTGG	ACCCCGCACC	AGGCTGTGGG	GTTTCTCAGA	TAActGGGCC	60
CCTGCGCTCA	GGAGGCCTTC	ACCCTCTGCT	CTGGGTAAAG	TTCATTGGAA	CAGAAAGAAA	120
TGGATTTATC	TGCTCTTCGC	GTTGAAGAAG	TACAAAATGT	CATTAATGCT	ATGCAGAAAA	180
TCTTAGAGTG	TCCCATCTGT	CTGGAGTTGA	TCAAGGAACC	TGTCTCCACA	AAGTGTGACC	240
ACATATTTTG	CAAATTTTGC	ATGCTGAAAC	TTCTCAACCA	GAAGAAAGGG	CCTTCACAGT	300
GTCTTTTATG	TAAGAATGAT	ATAACCAAAA	GGAGCCTACA	AGAAAGTACG	AGATTTAGTC	360
AACTTGTTGA	AGAGCTATTG	AAAATCATTT	GTGCTTTTCA	GCTTGACACA	GTTTGGAGT	420
ATGCAAACAG	CTATAATTTT	GCAAAAAAGG	AAAATAACTC	TCCTGAACAT	CTAAAAGATG	480
AAGTTTCTAT	CATCCAAAGT	ATGGGCTACA	GAAACCGTGC	CAAAGACTT	CTACAGAGTG	540
AACCCGAAAA	TCCTTCCTTG	CAGGAAACCA	GTCTCAGTGT	CCAActCTCT	AACCTTGGAA	600
CTGTGAGAAC	TCTGAGGACA	AAGCAGCGGA	TACAACCTCA	AAAGACGTCT	GTCTACATTG	660
AATTGGGATC	TGATTCTTCT	GAAGATACCG	TTAATAAGGC	AACTTATTGC	AGTGTGGGAG	720
ATCAAGAATT	GTTACAAATC	ACCCCTCAAG	GAACCAGGGA	TGAAATCAGT	TTGGATTCTG	780

CAAAAAAGGC	TGCTTGTGAA	TTTTCTGAGA	CGGATGTAAC	AAATACTGAA	CATCATCAAC	840
CCAGTAATAA	TGATTTGAAC	ACCACTGAGA	AGCGTGCAGC	TGAGAGGCAT	CCAGAAAAGT	900
ATCAGGGTAG	TTCTGTTTCA	AACTTGCATG	TGGAGCCATG	TGGCACAAAT	ACTCATGCCA	960
GCTCATTACA	GCATGAGAAC	AGCAGTTTAT	TACTCACTAA	AGACAGAATG	AATGTAGAAA	1020
AGGCTGAATT	CTGTAATAAA	AGCAAACAGC	CTGGCTTAGC	AAGGAGCCAA	CATAACAGAT	1080
GGGCTGGAAG	TAAGGAAACA	TGTAATGATA	GGCGGACTCC	CAGCACAGAA	AAAAAGGTAG	1140
ATCTGAATGC	TGATCCCCTG	TGTGAGAGAA	AAGAATGGAA	TAAGCAGAAA	CTGCCATGCT	1200
CAGAGAATCC	TAGAGATACT	GAAGATGTTT	CTTGATAAC	ACTAAATAGC	AGCATTCAGA	1260
AAGTTAATGA	GTGGTTTTCC	AGAAGTGATG	AACTGTTAGG	TTCTGATGAC	TCACATGATG	1320
GGGAGTCTGA	ATCAAATGCC	AAAGTAGCTG	ATGTATTGGA	CGTTCTAAAT	GAGGTAGATG	1380
AATATTCTGG	TTCTTCAGAG	AAAATAGACT	TACTGGCCAG	TGATCCTCAT	GAGGCTTTAA	1440
TATGTAAAAG	TGAAAGAGTT	CACTCCAAAT	CAGTAGAGAG	TAATATTGAA	GACAAAATAT	1500
TTGGGAAAAC	CTATCGGAAG	AAGGCAAGCC	TCCCCAACTT	AAGCCATGTA	ACTGAAAATC	1560
TAATTATAGG	AGCATTTGTT	ACTGAGCCAC	AGATAATACA	AGAGCGTCCC	CTCACAAATA	1620
AATTAAAGCG	TAAAAGGAGA	CCTACATCAG	GCCTTCATCC	TGAGGATTTT	ATCAAGAAAG	1680
CAGATTTGGC	AGTTCAAAAG	ACTCCTGAAA	TGATAAATCA	GGGAACAAAC	CAAACGGAGC	1740
AGAATGGTCA	AGTGATGAAT	ATTACTAATA	GTGGTCATGA	GAATAAAACA	AAAGGTGATT	1800
CTATTCAGAA	TGAGAAAAAT	CCTAACCCAA	TAGAATCACT	CGAAAAAGAA	TCTGCTTTCA	1860
AAACGAAAGC	TGAACCTATA	AGCAGCAGTA	TAAGCAATAT	GGAACCTGAA	TTAAATATCC	1920
ACAATTCAAA	AGCACCTAAA	AAGAATAGGC	TGAGGAGGAA	GTCTTCTACC	AGGCATATTC	1980

ATGCGCTTGA	ACTAGTAGTC	AGTAGAAATC	TAAGCCCACC	TAATTGTACT	GAATTGCAAA	2040
TTGATAGTTG	TTCTAGCAGT	GAAGAGATAA	AGAAAAAAAA	GTACAACCAA	ATGCCAGTCA	2100
GGCACAGCAG	AAACCTACAA	CTCATGGAAG	GTAAAGAACC	TGCAACTGGA	GCCAAGAAGA	2160
GTAACAAGCC	AAATGAACAG	ACAAGTAAAA	GACATGACAG	CGATACTTTC	CCAGAGCTGA	2220
AGTTAACAAA	TGCACCTGGT	TCTTTTACTA	AGTGTTCAAA	TACCAGTGAA	CTTAAAGAAT	2280
TTGTCAATCC	TAGCCTTCCA	AGAGAAGAAA	AAGAAGAGAA	ACTAGAAACA	GTTAAAGTGT	2340
CTAATAATGC	TGAAGACCCC	AAAGATCTCA	TGTTAAGTGG	AGAAAGGGTT	TTGCAAACTG	2400
AAAGATCTGT	AGAGAGTAGC	AGTATTTTCT	TGGTACCTGG	TACTGATTAT	GGCACTCAGG	2460
AAAGTATCTC	GTTACTGGAA	GTTAGCACTC	TAGGGAAGGC	AAAAACAGAA	CCAAATAAAT	2520
GTGTGAGTCA	GTGTGCAGCA	TTTGAAAACC	CCAAGGGACT	AATTCATGGT	TGTTCCAAAG	2580
ATAATAGAAA	TGACACAGAA	GGCTTTAAGT	ATCCATTGGG	ACATGAAGTT	AACCACAGTC	2640
GGGAAACAAG	CATAGAAATG	GAAGAAAGTG	AACTTGATGC	TCAGTATTTG	CAGAATACAT	2700
TCAAGGTTTC	AAAGCGCCAG	TCATTTGCTC	TGTTTTCAAA	TCCAGGAAAT	GCAGAAGAGG	2760
AATGTGCAAC	ATTCTCTGCC	CACTCTGGGT	CCTTAAAGAA	ACAAAGTCCA	AAAGTCACTT	2820
TTGAATGTGA	ACAAAAGGAA	GAAAATCAAG	GAAAGAATGA	GTCTAATATC	AAGCCTGTAC	2880
AGACAGTTAA	TATCACTGCA	GGCTTTCCTG	TGGTTGGTCA	GAAAGATAAG	CCAGTTGATA	2940
ATGCCAAATG	TAGTATCAAA	GGAGGCTCTA	GGTTTTGTCT	ATCATCTCAG	TTCAGAGGCA	3000
ACGAAACTGG	ACTCATTACT	CCAAATAAAC	ATGGACTTTT	ACAAAACCCA	TATCGTATAC	3060
CACCACTTTT	TCCCATCAAG	TCATTTGTTA	AACTAAATG	TAAGAAAAAT	CTGCTAGAGG	3120
AAAACCTTGA	GGAACATTCA	ATGTCACCTG	AAAGAGAAAT	GGGAAATGAG	AACATTCCAA	3180

GTACAGTGAG	CACAATTAGC	CGTAATAACA	TTAGAGAAAA	TGTTTTTAAA	GAAGCCAGCT	3240
CAAGCAATAT	TAATGAAGTA	GGTCCAGTA	CTAATGAAGT	GGGCTCCAGT	ATTAATGAAA	3300
TAGGTTCCAG	TGATGAAAAC	ATTCAAGCAG	AACTAGGTAG	AAACAGAGGG	CCAAAATTGA	3360
ATGCTATGCT	TAGATTAGGG	GTTTGCAAC	CTGAGGTCTA	TAAACAAAGT	CTTCCTGGAA	3420
GTAATTGTAA	GCATCCTGAA	ATAAAAAAGC	AAGAATATGA	AGAAGTAGTT	CAGACTGTTA	3480
ATACAGATTT	CTCTCCATAT	CTGATTTTCT	ATAACTTAGA	ACAGCCTATG	GGAAGTAGTC	3540
ATGCATCTCA	GGTTTGTTCT	GAGACACCTG	ATGACCTGTT	AGATGATGGT	GAAATAAAGG	3600
AAGATACTAG	TTTTGCTGAA	AATGACATTA	AGGAAAGTTC	TGCTGTTTTT	AGCAAAAGCG	3660
TCCAGAAAGG	AGAGCTTAGC	AGGAGTCCTA	GCCCTTTCAC	CCATACACAT	TTGGCTCAGG	3720
GTTACCGAAG	AGGGGCCAAG	AAATTAGAGT	CCTCAGAAGA	GAACTTATCT	AGTGAGGATG	3780
AAGAGCTTCC	CTGCTTCCAA	CACTTGTTAT	TTGGTAAAGT	AAACAATATA	CCTTCTCAGT	3840
CTACTAGGCA	TAGCACCGTT	GCTACCGAGT	GTCTGTCTAA	GAACACAGAG	GAGAATTTAT	3900
TATCATTGAA	GAATAGCTTA	AATGACTGCA	GTAACCAGGT	AATATTGGCA	AAGGCATCTC	3960
AGGAACATCA	CCTTAGTGAG	GAAACAAAAT	GTTCTGCTAG	CTTGTTTTCT	TCACAGTGCA	4020
GTGAATTGGA	AGACTTGACT	GCAAATACAA	ACACCCAGGA	TCCTTTCTTG	ATTGGTTCTT	4080
CCAAACAAAT	GAGGCATCAG	TCTGAAAGCC	AGGGAGTTGG	TCTGAGTGAC	AAGGAATTGG	4140
TTTCAGATGA	TGAAGAAAGA	GGAACGGGCT	TGGAAGAAAA	TAATCAAGAA	GAGCAAAGCA	4200
TGGATTCAAA	CTTAGGTGAA	GCAGCATCTG	GGTGTGAGAG	TGAAACAAGC	GTCTCTGAAG	4260
ACTGCTCAGG	GCTATCCTCT	CAGAGTGACA	TTTAAACCAC	TCAGCAGAGG	GATACCATGC	4320
AACATAACCT	GATAAAGCTC	CAGCAGGAAA	TGGCTGAACT	AGAAGCTGTG	TTAGAACAGC	4380

ATGGGAGCCA	GCCTTCTAAC	AGCTACCCTT	CCATCATAAG	TGACTCTTCT	GCCCTTGAGG	4440
ACCTGCGAAA	TCCAGAACAA	AGCACATCAG	AAAAAGCAGT	ATTAACTTCA	CAGAAAAGTA	4500
GTGAATACCC	TATAAGCCAG	AATCCAGAAG	GCCTTTCTGC	TGACAAGTTT	GAGGTGTCTG	4560
CAGATAGTTC	TACCAGTAAA	AATAAAGAAC	CAGGAGTGGA	AAGGTCATCC	CCTTCTAAAT	4620
GGCCATCATT	AGATGATAGG	TGGTACATGC	ACAGTTGCTC	TGGGAGTCTT	CAGAATAGAA	4680
ACTACCCATC	TCAAGAGGAG	CTCATTAAGG	TTGTTGATGT	GGAGGAGCAA	CAGCTGGAAG	4740
AGTCTGGGCC	ACACGATTTG	ACGGAAACAT	CTTACTTGCC	AAGGCAAGAT	CTAGAGGGAA	4800
CCCCTTACCT	GGAATCTGGA	ATCAGCCTCT	TCTCTGATGA	CCCTGAATCT	GATCCTTCTG	4860
AAGACAGAGC	CCCAGAGTCA	GCTCGTGTTG	GCAACATACC	ATCTTCAACC	TCTGCATTGA	4920
AAGTTCCCCA	ATTGAAAGTT	GCAGAATCTG	CCCAGAGTCC	AGCTGCTGCT	CATACTACTG	4980
ATACTGCTGG	GTATAATGCA	ATGGAAGAAA	GTGTGAGCAG	GGAGAAGCCA	GAATTGACAG	5040
CTTCAACAGA	AAGGGTCAAC	AAAAGAATGT	CCATGGTGGT	GTCTGGCCTG	ACCCCAGAAG	5100
AATTTATGCT	CGTGTACAAG	TTTGCCAGAA	AACACCACAT	CACTTTAACT	AATCTAATTA	5160
CTGAAGAGAC	TACTCATGTT	GTTATGAAAA	CAGATGCTGA	GTTTGTGTGT	GAACGGACAC	5220
TGAAATATTT	TCTAGGAATT	GCGGGAGGAA	AATGGGTAGT	TAGCTATTTT	TGGGTGACCC	5280
AGTCTATTAA	AGAAAGAAAA	ATGCTGAATG	AGCATGATTT	TGAAGTCAGA	GGAGATGTGG	5340
TCAATGGAAG	AAACCACCAA	GGTCCAAAGC	GAGCAAGAGA	ATCCCAGGAC	AGAAAGATCT	5400
TCAGGGGGCT	AGAAATCTGT	TGCTATGGGC	CCTTCACCAA	CATGCCACAC	GATCAACTGG	5460
AATGGATGGT	ACAGCTGTGT	GGTGCTTCTG	TGGTGAAGGA	GCTTTCATCA	TTCACCCTTG	5520
GCACAGGTGT	CCACCCAATT	GTGGTTGTGC	AGCCAGATGC	CTGGACAGAG	GACAATGGCT	5580

TCCATGCAAT TGGGCAGATG TGTGAGGCAC CTGTGGTGAC CCGAGAGTGG GTGTTGGACA 5640
 GTGTAGCACT CTACCAGTGC CAGGAGCTGG ACACCTACCT GATACCCCAG ATCCCCCACA 5700
 GCCACTACTG A 5711

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1863 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

- (A) CHROMOSOME/SEGMENT: 17
- (B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met	Asp	Leu	Ser	Ala	Leu	Arg	Val	Glu	Glu	Val	Gln	Asn	Val	Ile	Asn
1				5					10					15	
Ala	Met	Gln	Lys	Ile	Leu	Glu	Cys	Pro	Ile	Cys	Leu	Glu	Leu	Ile	Lys
			20					25					30		
Glu	Pro	Val	Ser	Thr	Lys	Cys	Asp	His	Ile	Phe	Cys	Lys	Phe	Cys	Met
		35					40					45			
Leu	Lys	Leu	Leu	Asn	Gln	Lys	Lys	Gly	Pro	Ser	Gln	Cys	Pro	Leu	Cys
50						55						60			

Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
65 70 75 80

Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
85 90 95

Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
100 105 110

Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
115 120 125

Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
130 135 140

Pro Ser Leu Gln Glu Thr Ser Leu Ser Val Gln Leu Ser Asn Leu Gly
145 150 155 160

Thr Val Arg Thr Leu Arg Thr Lys Gln Arg Ile Gln Pro Gln Lys Thr
165 170 175

Ser Val Tyr Ile Glu Leu Gly Ser Asp Ser Ser Glu Asp Thr Val Asn
180 185 190

Lys Ala Thr Tyr Cys Ser Val Gly Asp Gln Glu Leu Leu Gln Ile Thr
195 200 205

Pro Gln Gly Thr Arg Asp Glu Ile Ser Leu Asp Ser Ala Lys Lys Ala
210 215 220

Ala Cys Glu Phe Ser Glu Thr Asp Val Thr Asn Thr Glu His His Gln
225 230 235 240

Pro Ser Asn Asn Asp Leu Asn Thr Thr Glu Lys Arg Ala Ala Glu Arg
245 250 255

His Pro Glu Lys Tyr Gln Gly Ser Ser Val Ser Asn Leu His Val Glu
260 265 270

Pro Cys Gly Thr Asn Thr His Ala Ser Ser Leu Gln His Glu Asn Ser
 275 280 285
 Ser Leu Leu Leu Thr Lys Asp Arg Met Asn Val Glu Lys Ala Glu Phe
 290 295 300
 Cys Asn Lys Ser Lys Gln Pro Gly Leu Ala Arg Ser Gln His Asn Arg
 305 310 315 320
 Trp Ala Gly Ser Lys Glu Thr Cys Asn Asp Arg Arg Thr Pro Ser Thr
 325 330 335
 Glu Lys Lys Val Asp Leu Asn Ala Asp Pro Leu Cys Glu Arg Lys Glu
 340 345 350
 Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
 355 360 365
 Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
 370 375 380
 Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
 385 390 395 400
 Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
 405 410 415
 Asn Glu Val Asp Glu Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
 420 425 430
 Ala Ser Asp Pro His Glu Ala Leu Ile Cys Lys Ser Glu Arg Val His
 435 440 445
 Ser Lys Ser Val Glu Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
 450 455 460
 Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
 465 470 475 480
 Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg

				485						490					495
Pro	Leu	Thr	Asn	Lys	Leu	Lys	Arg	Lys	Arg	Arg	Pro	Thr	Ser	Gly	Leu
			500					505					510		
His	Pro	Glu	Asp	Phe	Ile	Lys	Lys	Ala	Asp	Leu	Ala	Val	Gln	Lys	Thr
	515						520					525			
Pro	Glu	Met	Ile	Asn	Gln	Gly	Thr	Asn	Gln	Thr	Glu	Gln	Asn	Gly	Gln
	530					535					540				
Val	Met	Asn	Ile	Thr	Asn	Ser	Gly	His	Glu	Asn	Lys	Thr	Lys	Gly	Asp
545					550				555						560
Ser	Ile	Gln	Asn	Glu	Lys	Asn	Pro	Asn	Pro	Ile	Glu	Ser	Leu	Glu	Lys
				565					570					575	
Glu	Ser	Ala	Phe	Lys	Thr	Lys	Ala	Glu	Pro	Ile	Ser	Ser	Ser	Ile	Ser
			580					585						590	
Asn	Met	Glu	Leu	Glu	Leu	Asn	Ile	His	Asn	Ser	Lys	Ala	Pro	Lys	Lys
	595						600					605			
Asn	Arg	Leu	Arg	Arg	Lys	Ser	Ser	Thr	Arg	His	Ile	His	Ala	Leu	Glu
	610					615					620				
Leu	Val	Val	Ser	Arg	Asn	Leu	Ser	Pro	Pro	Asn	Cys	Thr	Glu	Leu	Gln
625					630					635					640
Ile	Asp	Ser	Cys	Ser	Ser	Ser	Glu	Glu	Ile	Lys	Lys	Lys	Lys	Tyr	Asn
			645						650					655	
Gln	Met	Pro	Val	Arg	His	Ser	Arg	Asn	Leu	Gln	Leu	Met	Glu	Gly	Lys
			660					665					670		
Glu	Pro	Ala	Thr	Gly	Ala	Lys	Lys	Ser	Asn	Lys	Pro	Asn	Glu	Gln	Thr
	675						680					685			
Ser	Lys	Arg	His	Asp	Ser	Asp	Thr	Phe	Pro	Glu	Leu	Lys	Leu	Thr	Asn
	690					695					700				

Ala Pro Gly Ser Phe Thr Lys Cys Ser Asn Thr Ser Glu Leu Lys Glu
705 710 715 720

Phe Val Asn Pro Ser Leu Pro Arg Glu Glu Lys Glu Glu Lys Leu Glu
725 730 735

Thr Val Lys Val Ser Asn Asn Ala Glu Asp Pro Lys Asp Leu Met Leu
740 745 750

Ser Gly Glu Arg Val Leu Gln Thr Glu Arg Ser Val Glu Ser Ser Ser
755 760 765

Ile Ser Leu Val Pro Gly Thr Asp Tyr Gly Thr Gln Glu Ser Ile Ser
770 775 780

Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Glu Pro Asn Lys
785 790 795 800

Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
805 810 815

Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Glu Gly Phe Lys Tyr Pro
820 825 830

Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Glu Met Glu
835 840 845

Glu Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
850 855 860

Lys Arg Gln Ser Phe Ala Leu Phe Ser Asn Pro Gly Asn Ala Glu Glu
865 870 875 880

Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
885 890 895

Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys
900 905 910

Asn Glu Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
915 920 925

Phe	Pro	Val	Val	Gly	Gln	Lys	Asp	Lys	Pro	Val	Asp	Asn	Ala	Lys	Cys	930	935	940	
Ser	Ile	Lys	Gly	Gly	Ser	Arg	Phe	Cys	Leu	Ser	Ser	Gln	Phe	Arg	Gly	945	950	955	960
Asn	Glu	Thr	Gly	Leu	Ile	Thr	Pro	Asn	Lys	His	Gly	Leu	Leu	Gln	Asn	965	970	975	
Pro	Tyr	Arg	Ile	Pro	Pro	Leu	Phe	Pro	Ile	Lys	Ser	Phe	Val	Lys	Thr	980	985	990	
Lys	Cys	Lys	Lys	Asn	Leu	Leu	Glu	Glu	Asn	Phe	Glu	Glu	His	Ser	Met	995	1000	1005	
Ser	Pro	Glu	Arg	Glu	Met	Gly	Asn	Glu	Asn	Ile	Pro	Ser	Thr	Val	Ser	1010	1015	1020	
Thr	Ile	Ser	Arg	Asn	Asn	Ile	Arg	Glu	Asn	Val	Phe	Lys	Glu	Ala	Ser	1025	1030	1035	1040
Ser	Ser	Asn	Ile	Asn	Glu	Val	Gly	Ser	Ser	Thr	Asn	Glu	Val	Gly	Ser	1045	1050	1055	
Ser	Ile	Asn	Glu	Ile	Gly	Ser	Ser	Asp	Glu	Asn	Ile	Gln	Ala	Glu	Leu	1060	1065	1070	
Gly	Arg	Asn	Arg	Gly	Pro	Lys	Leu	Asn	Ala	Met	Leu	Arg	Leu	Gly	Val	1075	1080	1085	
Leu	Gln	Pro	Glu	Val	Tyr	Lys	Gln	Ser	Leu	Pro	Gly	Ser	Asn	Cys	Lys	1090	1095	1100	
His	Pro	Glu	Ile	Lys	Lys	Gln	Glu	Tyr	Glu	Glu	Val	Val	Gln	Thr	Val	1105	1110	1115	1120
Asn	Thr	Asp	Phe	Ser	Pro	Tyr	Leu	Ile	Ser	Asp	Asn	Leu	Glu	Gln	Pro	1125	1130	1135	

Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp	1140	1145	1150
Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn	1155	1160	1165
Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Lys Gly	1170	1175	1180
Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln	1185	1190	1195
Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu	1205	1210	1215
Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly	1220	1225	1230
Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala	1235	1240	1245
Thr Glu Cys Leu Ser Lys Asn Thr Glu Glu Asn Leu Leu Ser Leu Lys	1250	1255	1260
Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser	1265	1270	1275
Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe	1285	1290	1295
Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr	1300	1305	1310
Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser	1315	1320	1325
Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp	1330	1335	1340
Glu Glu Arg Gly Thr Gly Leu Glu Glu Asn Asn Gln Glu Glu Gln Ser	1345	1350	1355
			1360

Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Glu Ser Glu Thr
1365 -1370 1375

Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu
1380 1385 1390

Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln
1395 1400 1405

Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln
1410 1415 1420

Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu
1425 1430 1435 1440

Asp Leu Arg Asn Pro Glu Gln Ser Thr Ser Glu Lys Ala Val Leu Thr
1445 1450 1455

Ser Gln Lys Ser Ser Glu Tyr Pro Ile Ser Gln Asn Pro Glu Gly Leu
1460 1465 1470

Ser Ala Asp Lys Phe Glu Val Ser Ala Asp Ser Ser Thr Ser Lys Asn
1475 1480 1485

Lys Glu Pro Gly Val Glu Arg Ser Ser Pro Ser Lys Cys Pro Ser Leu
1490 1495 1500

Asp Asp Arg Trp Tyr Met His Ser Cys Ser Gly Ser Leu Gln Asn Arg
1505 1510 1515 1520

Asn Tyr Pro Ser Gln Glu Glu Leu Ile Lys Val Val Asp Val Glu Glu
1525 1530 1535

Gln Gln Leu Glu Glu Ser Gly Pro His Asp Leu Thr Glu Thr Ser Tyr
1540 1545 1550

Leu Pro Arg Gln Asp Leu Glu Gly Thr Pro Tyr Leu Glu Ser Gly Ile
1555 1560 1565

Ser Leu Phe Ser Asp Asp Pro Glu Ser Asp Pro Ser Glu Asp Arg Ala

1570	1575	1580
Pro Glu Ser Ala Arg Val Gly Asn Ile Pro Ser Ser Thr Ser Ala Leu		
1585	1590	1595 1600
Lys Val Pro Gln Leu Lys Val Ala Glu Ser Ala Gln Ser Pro Ala Ala		
1605	1610	1615
Ala His Thr Thr Asp Thr Ala Gly Tyr Asn Ala Met Glu Glu Ser Val		
1620	1625	1630
Ser Arg Glu Lys Pro Glu Leu Thr Ala Ser Thr Glu Arg Val Asn Lys		
1635	1640	1645
Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu		
1650	1655	1660
Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile		
1665	1670	1675 1680
Thr Glu Glu Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val		
1685	1690	1695
Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp		
1700	1705	1710
Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met		
1715	1720	1725
Leu Asn Glu His Asp Phe Glu Val Arg Gly Asp Val Val Asn Gly Arg		
1730	1735	1740
Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile		
1745	1750	1755 1760
Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro		
1765	1770	1775
Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val		
1780	1785	1790

Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
 1795 1800 1805
 Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
 1810 1815 1820

 Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
 1825 1830 1835 1840

 Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
 1845 1850 1855

 Gln Ile Pro His Ser His Tyr
 1860

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5711 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

- (A) CHROMOSOME/SEGMENT: 17
- (B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

AGCTCGCTGA	GACTTCCTGG	ACCCCGCACC	AGGCTGTGGG	GTTTCTCAGA	TAAGTGGGCC	60
CCTGCGCTCA	GGAGGCCTTC	ACCCTCTGCT	CTGGGTAAAG	TTCATTGGAA	CAGAAAGAAA	120
TGGATTTATC	TGCTCTTCGC	GTTGAAGAAG	TACAAAATGT	CATTAATGCT	ATGCAGAAAA	180
TCTTAGAGTG	TCCCATCTGT	CTGGAGTTGA	TCAAGGAACC	TGTCTCCACA	AAGTGTGACC	240
ACATATTTTG	CAAATTTTGC	ATGCTGAAAC	TTCTCAACCA	GAAGAAAGGG	CCTTCACAGT	300
GTCCTTTATG	TAAGAATGAT	ATAACCAAAA	GGAGCCTACA	AGAAAGTACG	AGATTTAGTC	360
AACTTGTTGA	AGAGCTATTG	AAAATCATTT	GTGCTTTTCA	GCTTGACACA	GGTTTGGAGT	420
ATGCAAACAG	CTATAATTTT	GCAAAAAAGG	AAAATAACTC	TCCTGAACAT	CTAAAAGATG	480
AAGTTTCTAT	CATCCAAAGT	ATGGGCTACA	GAAACCGTGC	CAAAAGACTT	CTACAGAGTG	540
AACCCGAAAA	TCCTTCCTTG	CAGGAAACCA	GTCTCAGTGT	CCAACCTCTCT	AACCTTGGA	600
CTGTGAGAAC	TCTGAGGACA	AAGCAGCGGA	TACAACCTCA	AAAGACGTCT	GTCTACATTG	660
AATTGGGATC	TGATTCTTCT	GAAGATACCG	TTAATAAGGC	AACTTATTGC	AGTGTGGGAG	720
ATCAAGAATT	GTTACAAATC	ACCCCTCAAG	GAACCAGGGA	TGAAATCAGT	TTGGATTCTG	780
CAAAAAAGGC	TGCTTGTGAA	TTTTCTGAGA	CGGATGTAAC	AAATACTGAA	CATCATCAAC	840
CCAGTAATAA	TGATTTGAAC	ACCACTGAGA	AGCGTGCAGC	TGAGAGGCAT	CCAGAAAAGT	900
ATCAGGGTAG	TTCTGTTTCA	AACTTGCATG	TGGAGCCATG	TGGCACAAAT	ACTCATGCCA	960
GCTCATTACA	GATGAGAAC	AGCAGTTTAT	TACTCACTAA	AGACAGAATG	AATGTAGAAA	1020
AGGCTGAATT	CTGTAATAAA	AGCAAACAGC	CTGGCTTAGC	AAGGAGCCAA	CATAACAGAT	1080
GGGCTGGAAG	TAAGGAAACA	TGTAATGATA	GGCGGACTCC	CAGCACAGAA	AAAAAGGTAG	1140
ATCTGAATGC	TGATCCCCTG	TGTGAGAGAA	AAGAATGGAA	TAAGCAGAAA	CTGCCATGCT	1200

CAGAGAATCC	TAGAGATACT	GAAGATGTTT	CTTGGATAAC	ACTAAATAGC	AGCATTCAGA	1260
AAGTTAATGA	GTGGTTTTCC	AGAAGTGATG	AACTGTTAGG	TTCTGATGAC	TCACATGATG	1320
GGGAGTCTGA	ATCAAATGCC	AAAGTAGCTG	ATGTATTGGA	CGTTCTAAAT	GAGGTAGATG	1380
AATATTCTGG	TTCTTCAGAG	AAAATAGACT	TACTGGCCAG	TGATCCTCAT	GAGGCTTTAA	1440
TATGTAAAAG	TGAAAGAGTT	CACTCCAAAT	CAGTAGAGAG	TAATATTGAA	GACAAAATAT	1500
TTGGGAAAAC	CTATCGGAAG	AAGGCAAGCC	TCCCCAACTT	AAGCCATGTA	ACTGAAAATC	1560
TAATTATAGG	AGCATTTGTT	ACTGAGCCAC	AGATAATACA	AGAGCGTCCC	CTCACAAATA	1620
AATTAAAGCG	TAAAAGGAGA	CCTACATCAG	GCCTTCATCC	TGAGGATTTT	ATCAAGAAAG	1680
CAGATTTGGC	AGTTCAAAAG	ACTCCTGAAA	TGATAAATCA	GGGAACCTAAC	CAAACGGAGC	1740
AGAATGGTCA	AGTGATGAAT	ATTACTAATA	GTGGTCATGA	GAATAAAACA	AAAGGTGATT	1800
CTATTCAGAA	TGAGAAAAAT	CCTAACCCAA	TAGAATCACT	CGAAAAAGAA	TCTGCTTTCA	1860
AAACGAAAGC	TGAACCTATA	AGCAGCAGTA	TAAGCAATAT	GGAACCTCGAA	TTAAATATCC	1920
ACAATTCAAA	AGCACCTAAA	AAGAATAGGC	TGAGGAGGAA	GTCTTCTACC	AGGCATATTC	1980
ATGCGCTTGA	ACTAGTAGTC	AGTAGAAAATC	TAAGCCCACC	TAATTGTACT	GAATTGCAAA	2040
TTGATAGTTG	TTCTAGCAGT	GAAGAGATAA	AGAAAAAATA	GTACAACCAA	ATGCCAGTCA	2100
GGCACAGCAG	AAACCTACAA	CTCATGGAAG	GTAAAGAACC	TGCAACTGGA	GCCAAGAAGA	2160
GTAACAAGCC	AAATGAACAG	ACAAGTAAAA	GACATGACAG	TGATACTTTC	CCAGAGCTGA	2220
AGTTAACAAA	TGCACCTGGT	TCTTTTACTA	AGTGTTCAAA	TACCAGTGAA	CTTAAAGAAT	2280
TTGTCAATCC	TAGCCTTCCA	AGAGAAGAAA	AAGAAGAGAA	ACTAGAAACA	GTTAAAGTGT	2340
CTAATAATGC	TGAAGACCCC	AAAGATCTCA	TGTTAAGTGG	AGAAAGGGTT	TTGCAAACCTG	2400

AAAGATCTGT	AGAGAGTAGC	AGTATTTTAC	TGGTACCTGG	TACTGATTAT	GGCACTCAGG	2460
AAAGTATCTC	GTTACTGGAA	GTTAGCACTC	TAGGGAAGGC	AAAAACAGAA	CCAAATAAAT	2520
GTGTGAGTCA	GTGTGCAGCA	TTTGAAAACC	CCAAGGGACT	AATTCATGGT	TGTTCCAAAG	2580
ATAATAGAAA	TGACACAGAA	GGCTTTAAGT	ATCCATTGGG	ACATGAAGTT	AACCACAGTC	2640
GGGAAACAAG	CATAGAAATG	GAAGAAAGTG	AACTTGATGC	TCAGTATTTG	CAGAATACAT	2700
TCAAGGTTTC	AAAGCGCCAG	TCATTTGCTC	TGTTTTCAAA	TCCAGGAAAT	GCAGAAGAGG	2760
AATGTGCAAC	ATTCTCTGCC	CACTCTGGGT	CCTTAAAGAA	ACAAAGTCCA	AAAGTCACTT	2820
TTGAATGTGA	ACAAAAGGAA	GAAAATCAAG	GAAAGAATGA	GTCTAATATC	AAGCCTGTAC	2880
AGACAGTTAA	TATCACTGCA	GGCTTTCCTG	TGGTTGGTCA	GAAAGATAAG	CCAGTTGATA	2940
ATGCCAAATG	TAGTATCAAA	GGAGGCTCTA	GGTTTTGTCT	ATCATCTCAG	TTCAGAGGCA	3000
ACGAAACTGG	ACTCATTACT	CCAAATAAAC	ATGGACTTTT	ACAAAACCCA	TATCGTATAC	3060
CACCACTTTT	TCCCATCAAG	TCATTTGTTA	AACTAAATG	TAAGAAAAAT	CTGCTAGAGG	3120
AAAAC TTGA	GGAACATTCA	ATGTCACCTG	AAAGAGAAAT	GGGAAATGAG	AACATTCCAA	3180
GTACAGTGAG	CACAATTAGC	CGTAATAACA	TTAGAGAAAA	TGTTTTTTAA	GGAGCCAGCT	3240
CAAGCAATAT	TAATGAAGTA	GGTTCCAGTA	CTAATGAAGT	GGGCTCCAGT	ATTAATGAAA	3300
TAGGTTCCAG	TGATGAAAAC	ATTCAAGCAG	AACTAGGTAG	AAACAGAGGG	CCAAAATTGA	3360
ATGCTATGCT	TAGATTAGGG	GTTTTGCAAC	CTGAGGTCTA	TAAACAAAGT	CTTCCTGGAA	3420
GTAATTGTAA	GCATCCTGAA	ATAAAAAAGC	AAGAATATGA	AGAAGTAGTT	CAGACTGTTA	3480
ATACAGATTT	CTCTCCATAT	CTGATTTTCA	ATAACTTAGA	ACAGCCTATG	GGAAGTAGTC	3540
ATGCATCTCA	GGTTTGTTCT	GAGACACCTG	ATGACCTGTT	AGATGATGGT	GAAATAAAGG	3600

AAGATACTAG	TTTTGCTGAA	AATGACATTA	AGGAAAGTTC	TGCTGTTTTT	AGCAAAAGCG	3660
TCCAGAGAGG	AGAGCTTAGC	AGGAGTCCTA	GCCCTTTCAC	CCATACACAT	TTGGCTCAGG	3720
GTTACCGAAG	AGGGGCCAAG	AAATTAGAGT	CCTCAGAAGA	GAACTTATCT	AGTGAGGATG	3780
AAGAGCTTCC	CTGCTTCCAA	CACTTGTTAT	TTGGTAAAGT	AAACAATATA	CCTTCTCAGT	3840
CTACTAGGCA	TAGCACCGTT	GCTACCGAGT	GTCTGTCTAA	GAACACAGAG	GAGAATTTAT	3900
TATCATTGAA	GAATAGCTTA	AATGACTGCA	GTAACCAGGT	AATATTGGCA	AAGGCATCTC	3960
AGGAACATCA	CCTTAGTGAG	GAAACAAAAT	GTTCTGCTAG	CTTGTTTTCT	TCACAGTGCA	4020
GTGAATTGGA	AGACTTGACT	GCAAATACAA	ACACCCAGGA	TCCTTTCTTG	ATTGGTTCTT	4080
CCAAACAAAT	GAGGCATCAG	TCTGAAAGCC	AGGGAGTTGG	TCTGAGTGAC	AAGGAATTGG	4140
TTTCAGATGA	TGAAGAAAGA	GGAACGGGCT	TGGAAGAAAA	TAATCAAGAA	GAGCAAAGCA	4200
TGGATTCAAA	CTTAGGTGAA	GCAGCATCTG	GGTGTGAGAG	TGAAACAAGC	GTCTCTGAAG	4260
ACTGCTCAGG	GCTATCCTCT	CAGAGTGACA	TTTAAACCAC	TCAGCAGAGG	GATACCATGC	4320
AACATAACCT	GATAAAGCTC	CAGCAGGAAA	TGGCTGAACT	AGAAGCTGTG	TTAGAACAGC	4380
ATGGGAGCCA	GCCTTCTAAC	AGCTACCCTT	CCATCATAAG	TGACTCTTCT	GCCCTTGAGG	4440
ACCTGCGAAA	TCCAGAACAA	AGCACATCAG	AAAAAGCAGT	ATTAACTTCA	CAGAAAAGTA	4500
GTGAATACCC	TATAAGCCAG	AATCCAGAAG	GCCTTTCTGC	TGACAAGTTT	GAGGTGTCTG	4560
CAGATAGTTC	TACCAGTAAA	AATAAAGAAC	CAGGAGTGGA	AAGGTCATCC	CCTTCTAAAT	4620
GCCCATCATT	AGATGATAGG	TGGTACATGC	ACAGTTGCTC	TGGGAGTCTT	CAGAATAGAA	4680
ACTACCCATC	TCAAGAGGAG	CTCATTAAGG	TTGTTGATGT	GGAGGAGCAA	CAGCTGGAAG	4740
AGTCTGGGCC	ACACGATTTG	ACGGAAACAT	CTTACTTGCC	AAGGCAAGAT	CTAGAGGGAA	4800

CCCCTTACCT	GGAATCTGGA	ATCAGCCTCT	TCTCTGATGA	CCCTGAATCT	GATCCTTCTG	4860
AAGACAGAGC	CCCAGAGTCA	GCTCGTGTTG	GCAACATACC	ATCTTCAACC	TCTGCATTGA	4920
AAGTTCCCCA	ATTGAAAGTT	GCAGAATCTG	CCCAGGGTCC	AGCTGCTGCT	CATACTACTG	4980
ATACTGCTGG	GTATAATGCA	ATGGAAGAAA	GTGTGAGCAG	GGAGAAGCCA	GAATTGACAG	5040
CTTCAACAGA	AAGGGTCAAC	AAAAGAATGT	CCATGGTGGT	GTCTGGCCTG	ACCCCAGAAG	5100
AATTTATGCT	CGTGTACAAG	TTTGCCAGAA	AACACCACAT	CACTTTAACT	AATCTAATTA	5160
CTGAAGAGAC	TACTCATGTT	GTTATGAAAA	CAGATGCTGA	GTTTGTGTGT	GAACGGACAC	5220
TGAAATATTT	TCTAGGAATT	GCGGGAGGAA	AATGGGTAGT	TAGCTATTTT	TGGGTGACCC	5280
AGTCTATTAA	AGAAAGAAAA	ATGCTGAATG	AGCATGATTT	TGAAGTCAGA	GGAGATGTGG	5340
TCAATGGAAG	AAACCACCAA	GGTCCAAAGC	GAGCAAGAGA	ATCCCAGGAC	AGAAAGATCT	5400
TCAGGGGGCT	AGAAATCTGT	TGCTATGGGC	CCTTCACCAA	CATGCCCACA	GATCAACTGG	5460
AATGGATGGT	ACAGCTGTGT	GGTGCTTCTG	TGGTGAAGGA	GCTTTCATCA	TTCACCCTTG	5520
GCACAGGTGT	CCACCCAATT	GTGGTTGTGC	AGCCAGATGC	CTGGACAGAG	GACAATGGCT	5580
TCCATGCAAT	TGGGCAGATG	TGTGAGGCAC	CTGTGGTGAC	CCGAGAGTGG	GTGTTGGACA	5640
GTGTAGCACT	CTACCAGTGC	CAGGAGCTGG	ACACCTACCT	GATACCCCAG	ATCCCCCACA	5700
GCCACTACTG	A					5711

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1863 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(B) STRAIN: BRCA1

(viii) POSITION IN GENOME:

(A) CHROMOSOME/SEGMENT: 17

(B) MAP POSITION: 17q21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Asp Leu Ser Ala Leu Arg Val Glu Glu Val Gln Asn Val Ile Asn
1 5 10 15

Ala Met Gln Lys Ile Leu Glu Cys Pro Ile Cys Leu Glu Leu Ile Lys
20 25 30

Glu Pro Val Ser Thr Lys Cys Asp His Ile Phe Cys Lys Phe Cys Met
35 40 45

Leu Lys Leu Leu Asn Gln Lys Lys Gly Pro Ser Gln Cys Pro Leu Cys
50 55 60

Lys Asn Asp Ile Thr Lys Arg Ser Leu Gln Glu Ser Thr Arg Phe Ser
65 70 75 80

Gln Leu Val Glu Glu Leu Leu Lys Ile Ile Cys Ala Phe Gln Leu Asp
85 90 95

Thr Gly Leu Glu Tyr Ala Asn Ser Tyr Asn Phe Ala Lys Lys Glu Asn
100 105 110

Asn Ser Pro Glu His Leu Lys Asp Glu Val Ser Ile Ile Gln Ser Met
115 120 125

Gly Tyr Arg Asn Arg Ala Lys Arg Leu Leu Gln Ser Glu Pro Glu Asn
130 135 140

Pro	Ser	Leu	Gln	Glu	Thr	Ser	Leu	Ser-Val	Gln	Leu	Ser	Asn	Leu	Gly	145	150	155	160	
Thr	Val	Arg	Thr	Leu	Arg	Thr	Lys	Gln	Arg	Ile	Gln	Pro	Gln	Lys	Thr	165	170	175	
Ser	Val	Tyr	Ile	Glu	Leu	Gly	Ser	Asp	Ser	Ser	Glu	Asp	Thr	Val	Asn	180	185	190	
Lys	Ala	Thr	Tyr	Cys	Ser	Val	Gly	Asp	Gln	Glu	Leu	Leu	Gln	Ile	Thr	195	200	205	
Pro	Gln	Gly	Thr	Arg	Asp	Glu	Ile	Ser	Leu	Asp	Ser	Ala	Lys	Lys	Ala	210	215	220	
Ala	Cys	Glu	Phe	Ser	Glu	Thr	Asp	Val	Thr	Asn	Thr	Glu	His	His	Gln	225	230	235	240
Pro	Ser	Asn	Asn	Asp	Leu	Asn	Thr	Thr	Glu	Lys	Arg	Ala	Ala	Glu	Arg	245	250	255	
His	Pro	Glu	Lys	Tyr	Gln	Gly	Ser	Ser	Val	Ser	Asn	Leu	His	Val	Glu	260	265	270	
Pro	Cys	Gly	Thr	Asn	Thr	His	Ala	Ser	Ser	Leu	Gln	His	Glu	Asn	Ser	275	280	285	
Ser	Leu	Leu	Leu	Thr	Lys	Asp	Arg	Met	Asn	Val	Glu	Lys	Ala	Glu	Phe	290	295	300	
Cys	Asn	Lys	Ser	Lys	Gln	Pro	Gly	Leu	Ala	Arg	Ser	Gln	His	Asn	Arg	305	310	315	320
Trp	Ala	Gly	Ser	Lys	Glu	Thr	Cys	Asn	Asp	Arg	Arg	Thr	Pro	Ser	Thr	325	330	335	
Glu	Lys	Lys	Val	Asp	Leu	Asn	Ala	Asp	Pro	Leu	Cys	Glu	Arg	Lys	Glu	340	345	350	

Trp Asn Lys Gln Lys Leu Pro Cys Ser Glu Asn Pro Arg Asp Thr Glu
 355 360 365
 Asp Val Pro Trp Ile Thr Leu Asn Ser Ser Ile Gln Lys Val Asn Glu
 370 375 380
 Trp Phe Ser Arg Ser Asp Glu Leu Leu Gly Ser Asp Asp Ser His Asp
 385 390 395 400
 Gly Glu Ser Glu Ser Asn Ala Lys Val Ala Asp Val Leu Asp Val Leu
 405 410 415
 Asn Glu Val Asp Glu Tyr Ser Gly Ser Ser Glu Lys Ile Asp Leu Leu
 420 425 430
 Ala Ser Asp Pro His Glu Ala Leu Ile Cys Lys Ser Glu Arg Val His
 435 440 445
 Ser Lys Ser Val Glu Ser Asn Ile Glu Asp Lys Ile Phe Gly Lys Thr
 450 455 460
 Tyr Arg Lys Lys Ala Ser Leu Pro Asn Leu Ser His Val Thr Glu Asn
 465 470 475 480
 Leu Ile Ile Gly Ala Phe Val Thr Glu Pro Gln Ile Ile Gln Glu Arg
 485 490 495
 Pro Leu Thr Asn Lys Leu Lys Arg Lys Arg Arg Pro Thr Ser Gly Leu
 500 505 510
 His Pro Glu Asp Phe Ile Lys Lys Ala Asp Leu Ala Val Gln Lys Thr
 515 520 525
 Pro Glu Met Ile Asn Gln Gly Thr Asn Gln Thr Glu Gln Asn Gly Gln
 530 535 540
 Val Met Asn Ile Thr Asn Ser Gly His Glu Asn Lys Thr Lys Gly Asp
 545 550 555 560
 Ser Ile Gln Asn Glu Lys Asn Pro Asn Pro Ile Glu Ser Leu Glu Lys

Leu Leu Glu Val Ser Thr Leu Gly Lys Ala Lys Thr Glu Pro Asn Lys
785 790 795 800

Cys Val Ser Gln Cys Ala Ala Phe Glu Asn Pro Lys Gly Leu Ile His
805 810 815

Gly Cys Ser Lys Asp Asn Arg Asn Asp Thr Glu Gly Phe Lys Tyr Pro
820 825 830

Leu Gly His Glu Val Asn His Ser Arg Glu Thr Ser Ile Glu Met Glu
835 840 845

Glu Ser Glu Leu Asp Ala Gln Tyr Leu Gln Asn Thr Phe Lys Val Ser
850 855 860

Lys Arg Gln Ser Phe Ala Leu Phe Ser Asn Pro Gly Asn Ala Glu Glu
865 870 875 880

Glu Cys Ala Thr Phe Ser Ala His Ser Gly Ser Leu Lys Lys Gln Ser
885 890 895

Pro Lys Val Thr Phe Glu Cys Glu Gln Lys Glu Glu Asn Gln Gly Lys
900 905 910

Asn Glu Ser Asn Ile Lys Pro Val Gln Thr Val Asn Ile Thr Ala Gly
915 920 925

Phe Pro Val Val Gly Gln Lys Asp Lys Pro Val Asp Asn Ala Lys Cys
930 935 940

Ser Ile Lys Gly Gly Ser Arg Phe Cys Leu Ser Ser Gln Phe Arg Gly
945 950 955 960

Asn Glu Thr Gly Leu Ile Thr Pro Asn Lys His Gly Leu Leu Gln Asn
965 970 975

Pro Tyr Arg Ile Pro Pro Leu Phe Pro Ile Lys Ser Phe Val Lys Thr
980 985 990

Lys Cys Lys Lys Asn Leu Leu Glu Glu Asn Phe Glu Glu His Ser Met
995 1000 1005

Ser Pro Glu Arg Glu Met Gly Asn Glu Asn Ile Pro Ser Thr Val Ser
 1010 1015 1020
 Thr Ile Ser Arg Asn Asn Ile Arg Glu Asn Val Phe Lys Gly Ala Ser
 1025 1030 1035 1040
 Ser Ser Asn Ile Asn Glu Val Gly Ser Ser Thr Asn Glu Val Gly Ser
 1045 1050 1055
 Ser Ile Asn Glu Ile Gly Ser Ser Asp Glu Asn Ile Gln Ala Glu Leu
 1060 1065 1070
 Gly Arg Asn Arg Gly Pro Lys Leu Asn Ala Met Leu Arg Leu Gly Val
 1075 1080 1085
 Leu Gln Pro Glu Val Tyr Lys Gln Ser Leu Pro Gly Ser Asn Cys Lys
 1090 1095 1100
 His Pro Glu Ile Lys Lys Gln Glu Tyr Glu Glu Val Val Gln Thr Val
 1105 1110 1115 1120
 Asn Thr Asp Phe Ser Pro Tyr Leu Ile Ser Asp Asn Leu Glu Gln Pro
 1125 1130 1135
 Met Gly Ser Ser His Ala Ser Gln Val Cys Ser Glu Thr Pro Asp Asp
 1140 1145 1150
 Leu Leu Asp Asp Gly Glu Ile Lys Glu Asp Thr Ser Phe Ala Glu Asn
 1155 1160 1165
 Asp Ile Lys Glu Ser Ser Ala Val Phe Ser Lys Ser Val Gln Arg Gly
 1170 1175 1180
 Glu Leu Ser Arg Ser Pro Ser Pro Phe Thr His Thr His Leu Ala Gln
 1185 1190 1195 1200
 Gly Tyr Arg Arg Gly Ala Lys Lys Leu Glu Ser Ser Glu Glu Asn Leu
 1205 1210 1215
 Ser Ser Glu Asp Glu Glu Leu Pro Cys Phe Gln His Leu Leu Phe Gly

1220	1225	1230
Lys Val Asn Asn Ile Pro Ser Gln Ser Thr Arg His Ser Thr Val Ala		
1235	1240	1245
Thr Glu Cys Leu Ser Lys Asn Thr Glu Glu Asn Leu Leu Ser Leu Lys		
1250	1255	1260
Asn Ser Leu Asn Asp Cys Ser Asn Gln Val Ile Leu Ala Lys Ala Ser		
1265	1270	1275 1280
Gln Glu His His Leu Ser Glu Glu Thr Lys Cys Ser Ala Ser Leu Phe		
1285	1290	1295
Ser Ser Gln Cys Ser Glu Leu Glu Asp Leu Thr Ala Asn Thr Asn Thr		
1300	1305	1310
Gln Asp Pro Phe Leu Ile Gly Ser Ser Lys Gln Met Arg His Gln Ser		
1315	1320	1325
Glu Ser Gln Gly Val Gly Leu Ser Asp Lys Glu Leu Val Ser Asp Asp		
1330	1335	1340
Glu Glu Arg Gly Thr Gly Leu Glu Glu Asn Asn Gln Glu Glu Gln Ser		
1345	1350	1355 1360
Met Asp Ser Asn Leu Gly Glu Ala Ala Ser Gly Cys Glu Ser Glu Thr		
1365	1370	1375
Ser Val Ser Glu Asp Cys Ser Gly Leu Ser Ser Gln Ser Asp Ile Leu		
1380	1385	1390
Thr Thr Gln Gln Arg Asp Thr Met Gln His Asn Leu Ile Lys Leu Gln		
1395	1400	1405
Gln Glu Met Ala Glu Leu Glu Ala Val Leu Glu Gln His Gly Ser Gln		
1410	1415	1420
Pro Ser Asn Ser Tyr Pro Ser Ile Ile Ser Asp Ser Ser Ala Leu Glu		
1425	1430	1435 1440

Asp	Leu	Arg	Asn	Pro	Glu	Gln	Ser	Thr	Ser	Glu	Lys	Ala	Val	Leu	Thr	1445	1450	1455
Ser	Gln	Lys	Ser	Ser	Glu	Tyr	Pro	Ile	Ser	Gln	Asn	Pro	Glu	Gly	Leu	1460	1465	1470
Ser	Ala	Asp	Lys	Phe	Glu	Val	Ser	Ala	Asp	Ser	Ser	Thr	Ser	Lys	Asn	1475	1480	1485
Lys	Glu	Pro	Gly	Val	Glu	Arg	Ser	Ser	Pro	Ser	Lys	Cys	Pro	Ser	Leu	1490	1495	1500
Asp	Asp	Arg	Trp	Tyr	Met	His	Ser	Cys	Ser	Gly	Ser	Leu	Gln	Asn	Arg	1505	1510	1515
Asn	Tyr	Pro	Ser	Gln	Glu	Glu	Leu	Ile	Lys	Val	Val	Asp	Val	Glu	Glu	1525	1530	1535
Gln	Gln	Leu	Glu	Glu	Ser	Gly	Pro	His	Asp	Leu	Thr	Glu	Thr	Ser	Tyr	1540	1545	1550
Leu	Pro	Arg	Gln	Asp	Leu	Glu	Gly	Thr	Pro	Tyr	Leu	Glu	Ser	Gly	Ile	1555	1560	1565
Ser	Leu	Phe	Ser	Asp	Asp	Pro	Glu	Ser	Asp	Pro	Ser	Glu	Asp	Arg	Ala	1570	1575	1580
Pro	Glu	Ser	Ala	Arg	Val	Gly	Asn	Ile	Pro	Ser	Ser	Thr	Ser	Ala	Leu	1585	1590	1595
Lys	Val	Pro	Gln	Leu	Lys	Val	Ala	Glu	Ser	Ala	Gln	Gly	Pro	Ala	Ala	1605	1610	1615
Ala	His	Thr	Thr	Asp	Thr	Ala	Gly	Tyr	Asn	Ala	Met	Glu	Glu	Ser	Val	1620	1625	1630
Ser	Arg	Glu	Lys	Pro	Glu	Leu	Thr	Ala	Ser	Thr	Glu	Arg	Val	Asn	Lys	1635	1640	1645

Arg Met Ser Met Val Val Ser Gly Leu Thr Pro Glu Glu Phe Met Leu
 1650 1655 1660

Val Tyr Lys Phe Ala Arg Lys His His Ile Thr Leu Thr Asn Leu Ile
 1665 1670 1675 1680

Thr Glu Glu Thr Thr His Val Val Met Lys Thr Asp Ala Glu Phe Val
 1685 1690 1695

Cys Glu Arg Thr Leu Lys Tyr Phe Leu Gly Ile Ala Gly Gly Lys Trp
 1700 1705 1710

Val Val Ser Tyr Phe Trp Val Thr Gln Ser Ile Lys Glu Arg Lys Met
 1715 1720 1725

Leu Asn Glu His Asp Phe Glu Val Arg Gly Asp Val Val Asn Gly Arg
 1730 1735 1740

Asn His Gln Gly Pro Lys Arg Ala Arg Glu Ser Gln Asp Arg Lys Ile
 1745 1750 1755 1760

Phe Arg Gly Leu Glu Ile Cys Cys Tyr Gly Pro Phe Thr Asn Met Pro
 1765 1770 1775

Thr Asp Gln Leu Glu Trp Met Val Gln Leu Cys Gly Ala Ser Val Val
 1780 1785 1790

Lys Glu Leu Ser Ser Phe Thr Leu Gly Thr Gly Val His Pro Ile Val
 1795 1800 1805

Val Val Gln Pro Asp Ala Trp Thr Glu Asp Asn Gly Phe His Ala Ile
 1810 1815 1820

Gly Gln Met Cys Glu Ala Pro Val Val Thr Arg Glu Trp Val Leu Asp
 1825 1830 1835 1840

Ser Val Ala Leu Tyr Gln Cys Gln Glu Leu Asp Thr Tyr Leu Ile Pro
 1845 1850 1855

Gln Ile Pro His Ser His Tyr
 1860

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 2F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAAGTTGTCA TTTTATAAAC CTTT

24

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 2R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TGTCTTTTCT TCCCTAGTAT GT

22

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 3F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TCCTGACACA GCAGACATTT A

21

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 3R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGGATTTTC GTTCTCACTT A

21

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 5F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CTCTTAAGGG CAGTTGTGAG

20

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 5R-M13* primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TTCCTACTGT GGTGCTTCC

20

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 6/7F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTATTTTAG TGTCCTTAAA AGG

23

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 6R

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTTCATGGAC AGCACTTGAG TG

22

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 7F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CACAACAAAG AGCATACATA GGG

23

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 6/7R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TCGGGTTTAC TCTGTAGAAG

20

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic) -

(vi) ORIGINAL SOURCE:

(B) STRAIN: 8F1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TTCTCTTCAG GAGGAAAAGC A

21

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 8R1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GCTGCCTACC ACAAATACAA A

21

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 9F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CCACAGTAGA TGCTCAGTAA ATA

23

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 9R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TAGGAAAATA CCAGCTTCAT AGA

23

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 10F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TGGTCAGCTT TCTGTAATCG

20

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 10R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GTATCTACCC ACTCTCTTCT TCAG

24

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11AF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CCACCTCCAA GGTGTATCA

19

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11AR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

TGTTATGTTG GCTCCTTGCT

20

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11BF1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CACTAAAGAC AGAATGAATC TA

22

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11BR1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GAAGAACCAG AATATTCATC TA

22

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11CF1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TGATGGGGAG TCTGAATCAA

20

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11CR1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

TCTGCTTTCT TGATAAAATC CT

22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11DF1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

AGCGTCCCCT CACAAATAAA

20

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11DR1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TCAAGCGCAT GAATATGCCT

20

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11EF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTATAAGCAA TATGGAAGTC GA

22

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11ER primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TTAAGTTCACT GGTATTTGAA CA

23

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11FF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GACAGCGATA CTTTCCCAGA

20

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11FR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

TGGAACAACC ATGAATTAGT C

21

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11GF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GGAAGTTAGC ACTCTAGGGA

20

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11GR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GCAGTGATAT TAACTGTCTG TA

22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11HF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TGGGTCCTTA AAGAAACAAA GT

22

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11HR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TCAGGTGACA TTGAATCTTC C

21

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11IF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CCACTTTTTTC CCATCAAGTC A

21

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11IR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

TCAGGATGCT TACAATTACT TC

22

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11JF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CAAAATTGAA TGCTATGCTT AGA

23

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 11JR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TCGGTAACCC TGAGCCAAAT

20

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11KF primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GCAAAAGCGT CCAGAAAGGA

20

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11KR-1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TATTTGCAGT CAAGTCTTCC AA

22

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11LF-1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GTAATATTGG CAAAGGCATC T

21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 11LR primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TAAAATGTGC TCCCCAAAAG CA

22

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 12F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GTCCTGCCAA TGAGAAGAAA

20

(2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 12R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

TGTCAGCAAA CCTAAGAATG T

21

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 13F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

AATGGAAAGC TTCTCAAAGT A

21

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 13R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

ATGTTGGAGC TAGGTCCTTA C

21

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 14F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CTAACCTGAA TTATCACTAT CA

22

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 14R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GTGTATAAAT GCCTGTATGC A

21

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 15F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGGCTGCCCA GGAAGTATG

19

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 15R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

AACCAGAATA TCTTTATGTA GGA

23

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 16F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

AATTCTTAAC AGAGACCAGA AC

22

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 16R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

AAACTCTTT CCAGAATGTT GT

22

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 17F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTGTAGAACG TGCAGGATTG

20

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 17R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TCGCCTCATG TGGTTTTA

18

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 18F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GGCTCTTTAG CTTCTTAGGA C

21

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 18R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GAGACCATTT TCCCAGCATC

20

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 19F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CTGTCATTCT TCCTGTGCTC

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTGTAGAACG TGCAGGATTG

20

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 17R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

TCGCCTCATG TGGTTTTA

18

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 18F primer

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 20R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GGGAATCCAA ATTACACAGC

20

(2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: not relevant
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

- (B) STRAIN: 21F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

AAGCTCTTCC TTTTGTGAAAG TC

22

(2) INFORMATION FOR SEQ ID NO:66:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 22 base pairs
 - (B) TYPE: nucleic acid

- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 21R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GTAGAGAAAT AGAATAGCCT CT

22

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 22F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

TCCCATTGAG AGGTCTTGCT

20

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 22R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GAGAAGACTT CTGAGGCTAC

20

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 23F-1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

TGAAGTGACA GTTCCAGTAG T

21

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:
(B) STRAIN: 23R-1 primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

CATTTTAGCC ATTCATTCAA CAA

23

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 24F primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

ATGAATTGAC ACTAATCTCT GC

22

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(vi) ORIGINAL SOURCE:

(B) STRAIN: 24R primer

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GTAGCCAGGA CAGTAGAAGG A

21